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THE TOTAL SYNTHESIS OF RESERPINE*

R. B. WOODWARD, F. E. BADER, H. BICKEL, A. J. FREY and R. W. KIERSTEAD
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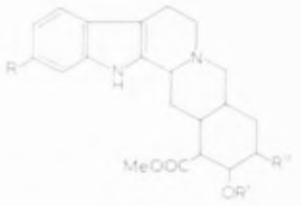
(*Received* 5 *October* 1957)

FOR centuries, the Indian snake-root, *Rauwolfia serpentina* Benth., has enjoyed a favorable reputation in its habitat as a valuable medicinal agent. The problem of defining the scope of its utility in terms of modern Western medical standards was complicated by the fact that the plant produces a very large number of closely related alkaloids, of which those present in larger relative measure are not those with the more interesting physiological properties.[1] Only five years ago, Schlittler first isolated reserpine, and demonstrated that this new alkaloid was largely responsible for the hypotensive activity associated with crude *Rauwolfia* extracts.[2] This discovery, and the remarkable effect which reserpine was subsequently found to exert upon the central nervous system, rapidly won for the alkaloid an important place in the treatment of hypertensive, nervous, and mental disorders.

Schlittler and his colleagues took structural studies in hand at once, and were soon able to propose for reserpine the structure (I : R = MeO, R′ = Me, R″ = 3,4,5-$(MeO)_3C_6H_2COO$).[3] Thus, it was early clear that reserpine is a member of the



I

great alkaloidal group of which yohimbine (I : R = R′ = R″ = H) is the prototype and oldest known member. There remained a stereochemical problem of no mean dimensions, and in view of the stereochemical abandon with which Nature has constructed the members of the yohimbine group—at least eight stereoisomers of yohimbine itself have so far been isolated from natural sources[1d]—few clues were at hand. But by summer of 1955, the Ciba group, and a number of independent investigators as well, had completed a series of elegant investigations which permitted the

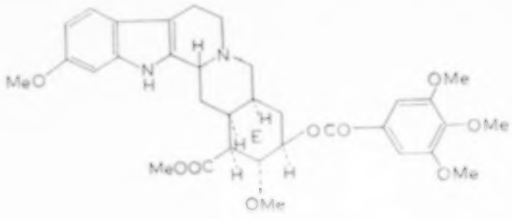
* For preliminary communications, see *J. Amer. Chem. Soc.* **78**, 2023, 2657 (1956).

[1a] A. Chatterjee *Fortschr. Chem. Org. Naturst.* **10**, 390 (1953); [b] A. Chatterjee, S. C. Pakrashi and G. Werner *Ibid.* **13**, 346 (1956); [c] E. Schlittler, J. A. Schneider and A. J. Plummer, *Angew. Chem.* **66**, 386 (1954); [d] J. E. Saxton, *Quart. Rev. Chem. Soc.* **10**, 128 (1956).

[2] J. M. Müller, E. Schlittler and H. J. Bein *Experientia* **8**, 338 (1952).

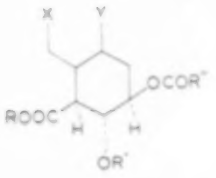
[3a] L. Dorfman, C. F. Huebner, H. B. MacPhillamy, E. Schlittler and A. F. St. André *Experientia* **9**, 368 (1953); [b] L. Dorfman, A. Furlenmeier, C. F. Huebner, R. Lucas, H. B. MacPhillamy, J. M. Mueller, E. Schlittler, R. Schwyzer and A. F. St. André *Helv. Chim. Acta* **37**, 59 (1954).

elaboration of the full structure (II) for reserpine.[4] The stage was now set for rational synthetic efforts.

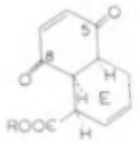


II

From the first, we looked upon the synthesis of reserpine as an exercise in stereochemistry. It will be noted that Ring E of the alkaloid is the site of an unusually heavy concentration of asymmetry. Indeed, five of the six asymmetric carbon atoms present are there disposed in a single consecutive chain. Consequently, it was our design to construct first an assemblage of the type (III), with the five groups attached



III



IV

to the single *cyclo*hexane ring suitably chosen in respect to function, and properly oriented.

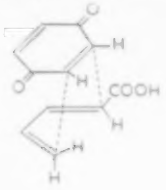
We chose as first step the reaction of vinylacrylic acid with quinone. The addition proceeded relatively smoothly in hot benzene solution, to give the adduct (IV : R = H). It will be noted that the newly formed six-membered ring of the adduct was destined to become Ring E of reserpine, that it contains already a felicitously placed carboxyl group, a double bond of good augury for the introduction of oxygen atoms at appropriate positions, *and three asymmetric carbon atoms properly oriented.* The well-known stereospecificity of the Diels–Alder reaction enabled us to assume with complete assurance that the two rings of the adduct were *cis*-locked, and it was only slightly less certain that the hydrogen atom at the third of the asymmetric centers created in the addition reaction would be on the same side of the molecular plane as those at the points of ring juncture. Thus, the only known form of vinylacrylic acid possesses a *trans* Δ^2 double bond,[5] and the combination of that isomer with quinone, proceeding through an intermediate (V) of the geometrical type generally accepted for the Diels–Alder reaction,[6] can lead only to an adduct with the stereochemistry defined in (IV).

[4a] C. F. Huebner, H. B. MacPhillamy, E. Schlittler and A. F. St. André *Experientia* **11**, 303 (1955); [b] E. Wenkert and L. H. Liu *Ibid* **11**, 302 (1955); [c] C. F. Huebner and E. Wenkert *J. Amer. Chem. Soc.* **77**, 4180 (1955); [d] P. A. Diassi, F. L. Weisenborn, C. M. Dylion and O. Wintersteiner *Ibid.* **77**, 4687 (1955); [e] E. E. van Tamelen and P. D. Hance *Ibid.* **77**, 4692 (1955).

[5] The configuration follows from the oxidation of the acid, by permanganate, to *dl*-tartaric acid (O. Doebner *Ber Dtsch. Chem. Ges.* **35**, 1141 (1902)).

[6] K. Alder, M. Schumacher and O. Wolff *Liebigs Ann.* **564**, 81 (1949); K. Alder *Ibid.* **571**, 157 (1951).

Some preliminary studies with the adduct (IV : R = H) served for the characterization of various of its functions. With diazomethane, the corresponding ester (IV : R = Me) was produced, albeit only in moderate yield; addition of diazomethane



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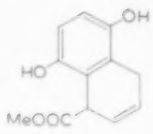

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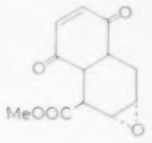
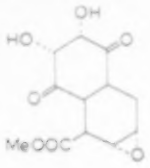
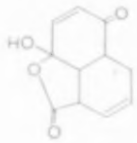


VII

to the carbon-carbon double bond of the ene-dione system was obviously a complicating factor. Attempts to prepare the ester by acid-catalyzed esterification with methanol led only to the aromatic isomer (VI), and emphasized the necessity for the use of gentle methods in effecting further elaboration of our key intermediate. The ester (IV : R = Me) was best prepared by the direct reaction of quinone with methyl vinylacrylate. The attack of perbenzoic acid on the ester was expected to, and did, involve preferential attack upon the isolated, and consequently relatively electron-rich, double bond, with formation of the oxide (VII). In its turn, the double bond of the ene-dione system was attacked by hydrogen peroxide in the presence of osmium tetroxide with the formation of the diol (VIII).



VIII



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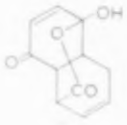
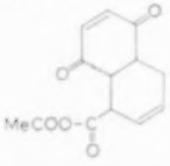
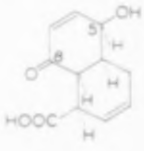


X

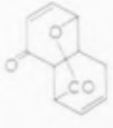
The structure of the adduct deserves some further comment in detail at this point. *A priori*, the possibility was present that one or another of the ring-chain tautomeric species (IX) or (X) might surpass the doubly ketonic structure (IV) in stability. In fact, no evidence for the presence of such molecules, even as minor participants in tautomeric equilibria could be found in the case of the free adduct. In particular, (IX) was easily excluded, through the absence of absorption in the infrared spectrum of the adduct in the 5·6–5·7 μ region. Further, the spectrum exhibited strong absorption of the characteristic carboxyl type at 2·8–4·2 μ, and the presence in the ultraviolet spectrum of bands at 224 and 355 mμ (log ε = 11,300 and 71) indicated that the system —CO—CH=CH—CO— was present.[7] Finally, with acetyl chloride and acetic anhydride, the adduct was converted to a simple



XI



XII



XIII

[7] Cf. D. H. R. Barton and A. S. Lindsay *J. Chem. Soc.* 2989 (1951).

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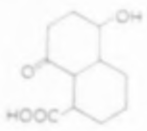
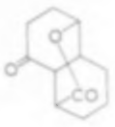
mixed anhydride (XI), rather than to a lactol acetate derived from (IX) or (X). None the less, the facts shortly to be detailed suggest that some kind of interaction between the carboxyl group and the carbonyl group at C.8 occurs in certain circumstances.*

We now wished to find a reaction which would differentiate the two similarly placed carbonyl groups in (IV ; R = H), and one was soon found in the reduction of the adduct by sodium borohydride in water to the dihydro derivative (XII). Although we were prepared to make use of the opportunity which would be presented by the selective reduction of *either* carbonyl group, it was of course necessary at this point to establish which of the groups had in fact suffered reduction in the case at hand. The issue was readily resolved through conversion of the reduction product into the corresponding transannular lactone (XIII), the six-membered nature of whose lactone ring was evident from the presence in its infrared spectrum of a strong band at 5·74 μ. Since there was a possibility that the concentration of divers functional groups in (XIII) might lead to abnormalities in the positions of infrared bands, the dihydro derivative also was converted by hydrogenation into the hexahydro compound (XIV), and thence into the saturated keto-lactone (XV), which could be prepared alternatively by the direct reduction of the doubly unsaturated lactone. The infrared



XIV



XV

XVI

spectrum of the saturated lactone possessed a normal ketonic carbonyl band at 5·85 μ, and a second band at 5·80 μ, characteristic of the carbonyl group of a six-membered lactone ring.

The formation of the lactone (XIII ⇌ XVI) may serve for the introduction of a number of stereochemical points of great importance. First, it will be noted (cf. XVI) that the lactone can be formed at all only if the hydroxy acid from which it was obtained possesses the structure (XII) in regard to all stereochemical details. Consequently, the experiment demonstrates rigorously that *the asymmetric carbon atoms of the original adduct are in fact oriented in the manner hitherto deduced only on theoretical grounds*. Secondly, it will be noted that the lactone does not form spontaneously from the hydroxy acid. This fact demonstrates that of the two possible conformations (XVII) and (XVIII), the hydroxy acid assumes the former, in which the groups attached to the ring skeleton are disposed in the energetically favorable *quasi*-equatorial orientation. Consequently, in order to bring about lactonization, energy must be put into the system in order to bring about conversion of the hydroxy

* The carbon atoms of the bicyclic derivatives in this paper are numbered according to the annexed scheme.

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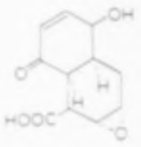
acid molecules into the less favored conformation (XVIII), with axially disposed carboxyl and hydroxyl groups. Conversely, it may be noted that *the co-operation of those groups in the formation of a lactone function serves to freeze the molecular framework in an otherwise relatively unfavorable conformation, with important stereochemical consequences for operations on the periphery of the molecule.* A third theoretical point of importance is brought to light by a consideration of the fact that the addition of hydrogen in the reduction of the carbonyl group at C.5 of the adduct (IV : R = H) takes place from the same side of the molecule on which the two bridgehead hydrogen atoms are located (cf. XVII). The known preference for the formation of equatorial hydroxyl groups in hydride reductions of relatively unhindered carbonyl groups[8] would have suggested in any case that (XII ⟹ XVII) would be formed, but it should be emphasized in addition that to the extent that steric factors are operative in directing the reduction, the same product would be expected. For, *all* cis *decalin derivatives*

XVII

XVIII



XIX

possess cage-like structures, to which access is severely obstructed on the concave face;[9] it will be clear from the subsequent narrative that we have made much use of this simple steric property of our *cis* decalin derivatives.

Before leaving the discussion of the dihydro adduct (XII), some further comment is necessary upon the selectivity of the reduction. Even in the presence of a large excess of the reducing reagent the carbonyl group at C.8 is not saturated. This result was hardly anticipated, nor is it even now entirely clear to what it should be attributed. Certain it is that the C.8 carbonyl group is much the more hindered of the two present; but sodium borohydride is not notably subject to ordinary steric effects, and it seems possible either that the carboxylate ion, proximate as it is to the relevant carbonyl group (cf. XVII), exerts electrostatic repulsion upon the borohydride ion, or perhaps interacts electronically with the carbonyl group in such wise as to effect the virtual saturation of the latter.

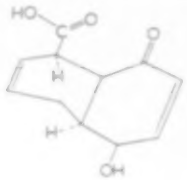
We turned now to the problem of introducing oxygen atoms at appropriate positions of our Ring E progenitor. Our expectation was realized that perbenzoic acid would attack the dihydroadduct (XII ⟹ XVII) on the convex face, and preferentially at the isolated double bond, with formation of the oxide (XIX). A point of much theoretical interest emerges from the fact that a similar preferential reaction could not be realized in the case of the lactone (XIII). In that case, oxidation by perbenzoic acid occurred relatively slowly, the consumption of oxidant did not

[9] The term *convex face* is used in the sequel for that side of *cis* decalin derivatives on which the *cis* bridgehead hydrogen atoms are located. The use of this designation, and the complementary *concave face* for the opposite side, obviates the ambiguities inherent in such phrases as "from the *top* side," and "attack from the *rear*."

[8] D. H. R. Barton *J. Chem. Soc.* 1027 (1953); H. R. Nace and G. L. O'Connor *J. Amer. Chem. Soc.* **73**, 5824 (1951); J. B. Umland and M. I. Jefraim *Ibid.* **78**, 2788 (1956).

cease after one mole, and no clearly defined products were isolated.* It is clear that in both cases, the *conjugated* double bond is relatively inert to cationoid oxidants as a result of electron withdrawal by the directly attached carbonyl group. The different behavior of the isolated double bonds in the two cases is attributable to the fact that in the lactone, the geometrical prerequisites for *electron release from the isolated double bond to the carboxyl carbonyl group* are better satisfied than in the acid. Thus, in the lactone the relevant carbonyl group is axially disposed, and the opportunity for overlap between the electron-deficient π orbital of that group and the π orbitals of the double bond is relatively favorable (cf. XX, arrow). In marked contrast,

XX



XXI

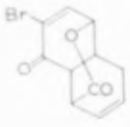
XXII

the equatorial orientation of the carboxyl group in the hydroxy acid provides little occasion for an analogous interaction (cf. XXI). The striking effects which can arise from similar interactions between non-bonded centers may be emphasized by reference to the carbonium ion (XXII), which is stabilized to such an extent by orbital overlap that the corresponding toluenesulfonate is solvolyzed one hundred billion times more rapidly than the saturated analog.[9]

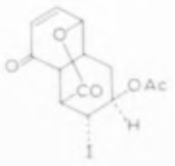
We considered, but regarded as unlikely, the possibility that the attack of perbenzoic acid on (XII) might lead directly to a hydroxy lactone of the type (XXIII).

* Further, very striking, evidence of the deactivation of the $\Delta^{2,3}$ double bond in the lactone (XIII) was found in the observation that the substance was converted by one mole of bromine to the α-bromo-α, β-unsaturated ketone (i).

On the other hand, preferential attack at the non-conjugated center of unsaturation was achieved with iodine and silver acetate in acetic acid, which converted the lactone into the iodoacetate (ii).



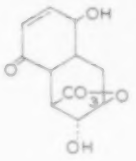
i



ii

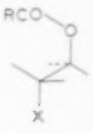
[9] S. Winstein, M. Shatavsky, C. Norton and R. B. Woodward *J. Amer. Chem. Soc.* **77**, 4183 (1955).

While it is true that unsaturated acids frequently undergo changes of the sort (XXIV → XXV) on attack by electron-deficient reagents, it is clear that the equatorial dispo-



XXIII

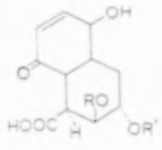
XXIV



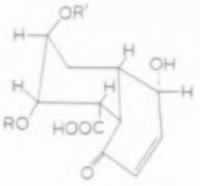
XXV

sition of the carboxyl group in the most stable conformational isomer of (XII ≡ XVII) places that function at such remove from the terminal carbon atom (C.3) of the double bond that a concerted reaction of the type under discussion cannot occur. Of course, the geometry of the unstable conformational isomer (XVIII) is favorable for the concerted reaction, and since conformational changes are no doubt rapid, the hydroxy lactone could be formed, if the relevant double bond ($\Delta^{2,3}$) of (XVIII) were more reactive than the corresponding unsaturated center in (XVII); but the discussion of the preceding paragraph indicates that the double bond with the adjacent axially oriented carboxyl group will be the *less* reactive of the pair.

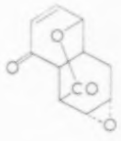
We now came to grips with the problem of opening the 2,3-oxide ring. The cleavage of the oxide ring of (XIX) by hydrolytic reagents would be expected to lead to a *trans* diol derivative of the undesirable stereostructure (XXVI), since it is well



XXVI



XXVII



XXVIII

known that the cleavage of cyclohexane oxides proceeds by preference with the formation of axial *trans* diols (cf. XXVII).[10] However, it was clear that the opening of the oxide could be forced to take the alternative desired direction if the molecule of (XIX) could be forced to assume the alternative conformation available to it as a *cis* decalin derivative. Our earlier experience with the lactonization of the simple hydroxy acid (XII) had shown us how this conformational change could be realized, and we next converted the oxide (XIX) into the corresponding lactone (XXVIII), by treatment with acetic anhydride and sodium acetate in benzene. We could now be

[10] D. H. R. Barton and R. C. Cookson *Quart. Rev. Chem. Soc.* **10**, 67 (1956).

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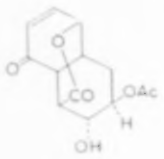
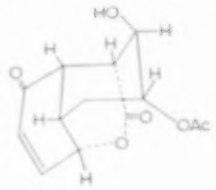
confident that the hydroxy acetate which we obtained from the oxide lactone by the action of boiling acetic acid had the desired structure (XXIX ≡ XXX). Indeed, in



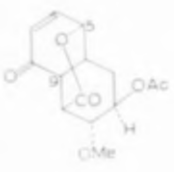
XXIX



XXX

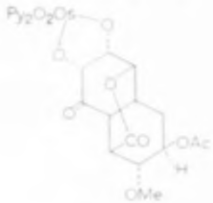
the latter, *we had in hand for the first time an intermediate in which the problem presented by the stereochemistry of Ring E of reserpine was solved.* Further, the hydroxy acetate possesses only one active hydrogen atom, and further progress toward an appropriate reserpine intermediate was readily achieved through conversion to the corresponding methyl ether (XXXI) by treatment with silver oxide and methyl iodide.*

The further elaboration of the methoxy acetate (XXXI) in the direction of an intermediate of the desired general type (III) required the removal of the oxygen atom at C.8, or the interpolation of a new methylene group between C.8 and C.9. No



XXXI

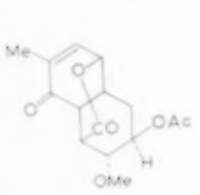
XXXII



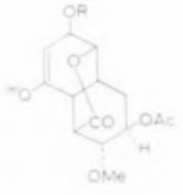
XXXIII

doubt one or the other of these objectives could have been realized, but very favorable developments in another direction supervened at this point, and this series was not carried beyond the oxide (XXXII) and the glycol osmate (XXXIII) prepared from

* The preparation of pure samples of the methoxy acetate (XXXI) was often attended by considerable difficulty. Careful chromatography of the crude product showed that it was contaminated with a homolog for which the structure (iii) is proposed (λ_{max} 234 mμ, as contrasted with λ_{max} 222 mμ for (XXXI)). The details of the course followed in the formation of (iii) have not been established, but it may be suggested that addition of an anion (perhaps MeO^- or AgO^-) to the conjugated double bond gives (iv), which is then



iii



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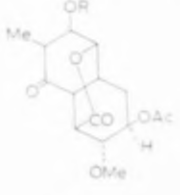


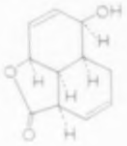
v

discharged by C-alkylation. Subsequent loss of ROH from the resulting (v), with formation of the observed product, would be unexceptional.

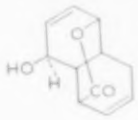
It may be noted that steric factors prohibit direct enolization of (XXXI), by proton migration from *either* C.5 or C.9.

the unsaturated ketone by treatment with alkaline hydrogen peroxide, and osmium tetroxide in pyridine respectively.

While the studies of the six-membered lactone intermediates just described were in progress, we were at the same time investigating the opportunities presented by a series of five-membered lactones, of which (XXXIV) may serve as the prototype.



XXXIV



XXXV

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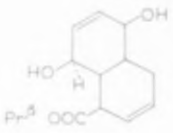
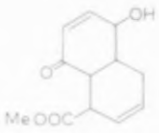
This substance was first encountered as the product of the reduction of the simple six-membered lactone (XIII) by aluminium *iso*propoxide in *iso*propanol. That it possessed the structure (XXXIV) rather than that of the proximate reduction product (XXXV) was clearly apparent from the presence in its infrared spectrum of a band at 5·68 μ. Since direct translactonization by attack of the hydroxyl group of (XXXV) upon the lactone carbonyl group is sterically improbable, it was necessary to presume that the lactone ring had first been cleaved by *iso*propanol with formation of an ester (XXXVI), from which the product (XXXIV) could be formed without difficulty.



XXXVI



XXXVII

This view received support when it was found that the ester (XXXVII), prepared from the corresponding acid (XII) by the action of diazomethane in dioxane* was, like the lactone (XIII), converted smoothly into (XXXIV) by aluminium *iso*propoxide in *iso*propanol. Finally, the five-membered lactone was found to be most simply preparable by the direct reduction of the ester adduct (IV : R = Me).

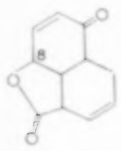
The hydroxy lactone (XXXIV) was readily oxidizable by chromic acid in acetic

* Like the adducts (IV), though less so, our compounds containing the system (vi) were susceptible to aromatization in the presence of strong acids. When an attempt was made to prepare the ester (XXXVII)

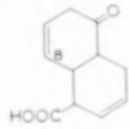
vi vii

by acid-catalyzed esterification of the corresponding acid, crude mixtures were obtained whose ultraviolet and infrared absorption was clearly indicative of the presence of substances containing the chromophore (vii). It is likely that the aromatization reaction involves prior enolization of the C.8 carbonyl group towards C.9; our qualitative observations suggest that substances such as the lactone (XXVIII) in which such enolization is sterically prohibited, are more resistant to aromatization than the enolizable analogues.

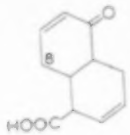
acid to the corresponding keto lactone (XXXVIII), which was found to be subject to remarkably facile reductive cleavage by zinc and acetic acid, with formation of the β,γ-unsaturated keto acid (XXXIX).* The latter was readily converted to



XXXVIII



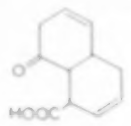
XXXIX



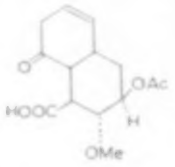
XL

the corresponding conjugated isomer (XL) when it was warmed with potassium acetate in alcohol. Clearly, these developments suggested a very simple possibility for the removal of the unwanted oxygen atom at C.8 in our intermediates, *provided that a representative of the five-membered lactone series suitably oxygenated at* C.2 *and* C.3 *could be found.* Experiments on the direct oxidation of the $\Delta^{2,3}$ double bond of the keto lactone (XXXVIII) were not promising since, as in the earlier studies with the six-membered lactone (XIII), perbenzoic acid did not differentiate satisfactorily between the two oxidizable portions of the molecule.† Thus, the reagent was consumed slowly, an integral number of moles of oxidant was not consumed,

* The α,β-unsaturated ketones of the six-membered lactone series, e.g., (XIII) and (XXXI), were also very readily reduced by zinc and acetic acid, with the formation of (viii) and (ix), respectively.



viii



ix

We suggest that the process involves attack of zinc on the oxygen atom of the ketonic carbonyl group (x, arrows).[11] The formation of the unstable β,γ-unsaturated ketone on discharge of the resulting complex

x xi

enolate (xi), *under essentially irreversible conditions,* is expected.

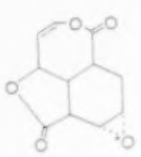
† As in the case of the six-membered lactone (XIII), (*vide supra*), the sluggishness of the $\Delta^{2,3}$ bond of (XXXVIII) is attributed to electron release from that center to a non-conjugated carbonyl group. The five-membered lactone may exist in one of two conformations; in view of the presence of three trigonal atoms in one ring, a decision in respect to the relative stabilities of the two conformational isomers is difficult, but in any event, in one of them, the lactone carbonyl group is axially oriented with respect to the $\Delta^{2,3}$-bond, as in (XIII), while in the other, the geometry is very favorable for interaction *between the* $\Delta^{2,3}$ *bond and the* C.5 *carbonyl group.*

It is worthy of note that the five-membered lactone (XXXVIII) further resembled the six-membered analogue (XIII) in that it was attacked at the unconjugated $\Delta^{2,3}$ double bond by iodine and silver acetate in acetic acid, with formation of the corresponding iodoacetate.

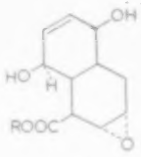
[11] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore *J. Amer. Chem. Soc.* **74**, 4225 (1952).

and the sole isolable product was a substance whose characteristic physical properties indicated clearly that it possessed the structure (XLI).

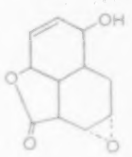
In these circumstances, it was natural to consider whether the oxide lactone (XXVIII), which was an important intermediate in our earlier series, could be converted into a representative of the five-membered lactone series through reduction



XLI

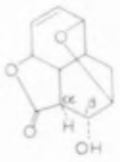


XLII

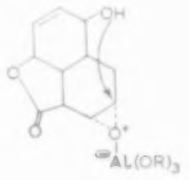


XLIII

by aluminium *iso*propoxide in *iso*propanol. We anticipated that the lactone would first be converted into an hydroxy ester of the type (XLII : R = Pr^{β}), that further change to an hydroxy lactone (XLIII) would then result, and were cognizant of the possibility that the latter might well be converted into an hydroxy ether (XLIV).



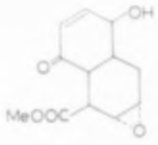
XLIV



XLV

For aluminium *iso*propoxide can function as an acidic reagent, capable of labilizing the oxide ring for intramolecular attack by a sterically favorably disposed hydroxyl group (cf. XLV, arrow). In the event, all of these changes did in fact occur, and yet another. The major product of the reaction was the unsaturated ether (XLVI). Clearly, the lactone carbonyl group of the presumed intermediate (XLIV) activates

XLVI



XLVII

the adjacent methine hydrogen, and permits a ready β elimination of the hydroxyl group. It may be noted that as in the simpler series, the ester (XLVII), prepared from the corresponding acid (XIX) by the action of diazomethane in dioxane, was likewise converted into the unsaturated ether (XLVI) on aluminium *iso*propoxide reduction.

We turn now to a discussion of the stereochemistry of the formation of the unsaturated ether (XLVI), and of the five-membered lactone series in general. First, it is clear that the reduction of the carbonyl group at C.8 in either the ester (XLVII), or the lactone (XXVIII), will involve addition at the convex face of the molecule, since in

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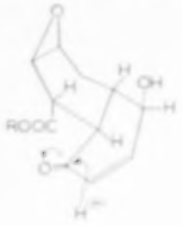
both compounds access to the carbonyl group at the concave face is very severely obstructed (cf. XLVIII and XLIX). Secondly, the preferred conformation (L) of



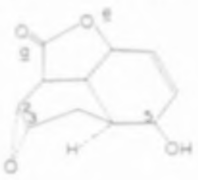
XLVIII

XLIX

L

the dihydroxy ester (XLII) which must be assumed as an intermediate in the processes leading to (XLVI) does not permit a concerted oxide opening with formation of the required 3,5 ether linkage. Indeed, cyclic ether formation at the ester stage should lead to a 2,8 oxide ring.* These considerations led us to conclude that *the formation of the* 3,5 *oxide bridge follows establishment of the five-membered lactone ring*. For the lactone oxide (XLIII), two alternative conformations, (LI) and (LII), are available, whose major difference, *vis-a-vis* energy, lies in the *quasi*-axial disposition of the

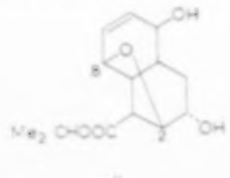
LI



LII

hydroxyl group at C.5 in one, and the *quasi*-equatorial orientation of the same group

* In the light of the above discussion, a dihydroxy ester $C_{14}H_{20}O_5$, which is a major by-product of the

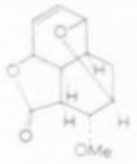


xii

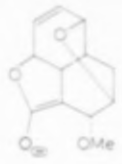
reaction, may well have the structure (xii).

in the other. Consequently, (LII), in which 3,5 oxide bridge formation is impossible, is undoubtedly the predominant species. However, the cleavage of the 2,3 oxide ring involves an increase in electron deficiency at C.2 and C.3, and factors similar to those which render the $\Delta^{2,3}$ double bond of the lactone (XX), *with an adjacent axial carbonyl group*, relatively inert to cationoid oxidants (*vide supra*) will oppose the opening of the ethylene oxide ring of (LII), as compared with that of (LI), whose adjacent carbonyl group is equatorial. The extent to which the concerted reaction occurs indicates that the greater reactivity of (LI) more than compensates for the position of the isomer as minor component in the conformational equilibrium.

The presence in the unsaturated ether (XLVI) of a double bond conjugated with a carbonyl group now suggested a new and simple possibility for the introduction of the required methoxyl group at C.2. When (XLVI) was treated with sodium methoxide in methanol, it was smoothly transformed into the methoxy ether (LIII). The

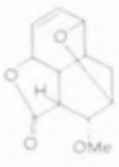


LIII

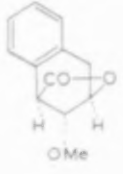


LIV

stereochemical factors attendant upon this change require comment. There was no doubt that methoxide ion would attack the molecule at the convex face, since the hindrance to access from the alternative direction which is present in all *cis* decalin derivatives was in this case rendered even more formidable by the 3,5 oxide bridge. On the other hand, discharge of the resulting anion (LIV) by a proton could *a priori* occur to give either of two isomers. Since the reaction was carried out under conditions which would in all likelihood lead to equilibration, with formation of the more stable of the two isomers, it was necessary to attempt to estimate whether the desired lactone (LIII), or the isomer (LV) would be more stable. The study of models pointed very strongly in one direction, but did not permit a conclusion of the rigorous sort which could be made, for example, in the case of the lactone (XIII). Thus, in the lactone (LIII) Ring E must assume the boat form. Further, it was possible, albeit with much strain, to construct models of the lactone (LV) with both carbocyclic rings in the chair conformation. Consequently, it was desirable to call upon generalized



LV



LVI

experience, which indicates that five-membered lactone rings fused to a six-membered ring are in all simple cases far more stable when the ring fusion is *cis* than when it is *trans*. Since our lactone was a very stable one, and we could discern in its molecule no special factors which could confer special stability on a *trans* fused bicyclic lactone system, we were confident that the substance had the desired structure (LIII). This

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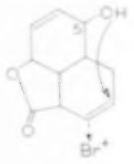
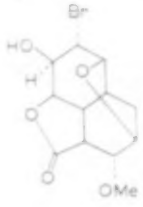
conclusion was confirmed experimentally when it was found that the methoxy lactone was converted by stannic chloride in acetyl chloride to a simple aromatic methoxy lactone of the structure (LVI); clearly the formation of the new five-membered lactone ring of (LVI) requires that the ether oxygen atom and the lactone carbonyl group of (LIII) be on the same side of the molecule.

In the methoxy ether (LIII) we now had a second, and relatively readily available intermediate containing all five of the asymmetric carbon atoms of Ring E of reserpine, properly oriented. Upon finding that the carbon-carbon double bond of the ether was markedly resistant to attack by bromine, we now foresaw the possibility of preparing that intermediate by a process even simpler than that just described. The considerations advanced above suggested that just as a 2,3 oxide in the five-membered lactone series was susceptible to concerted cleavage, so a double bond at that position should be susceptible to attack by an electron-deficient reagent with concerted intramolecular release of the electron deficiency in the resulting intermediate by the hydroxyl group at C.5 (cf. LVII, arrows), and indeed, when the simple doubly unsaturated lactone (XXXIV) was treated with bromine, preferably in an inert solvent, but even in methanol solution, the bromo lactone (LVIII) was produced. Not surprisingly, when the latter was treated with sodium methoxide in methanol, dehydrobromination occurred readily, and methanol was added to the double bond of the resulting conjugated lactone (XLVI), to give directly the familiar methoxy ether (LIII).



LVII

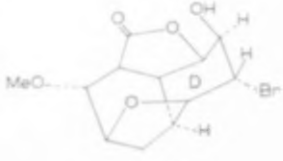
LVIII



LIX

We next turned our attention to modification of the upper ring of the intermediate (LIII). While the double bond in that substance was not attacked by bromine in chloroform or acetic acid at room temperature, aqueous N-bromosuccinimide in the presence of sulfuric acid at 80° readily converted the unsaturated ether to the bromohydrin (LIX). The structure of the bromohydrin was assigned on the following basis: (i) The conformation of the unsaturated ether is one (LX) in which

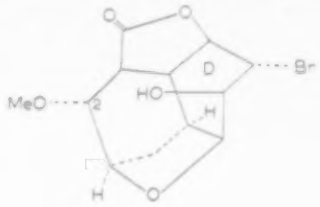
LX



LXI

the unsaturated ring (D) assumes the *quasi*-chair form and the other ring a (slightly distorted) boat form. (ii) Attack upon the molecule is initiated at the convex face by positive bromine. (iii) Therefore, the most readily accessible transition state for hypobromous acid addition is one which leads directly (cf. LX, arrows) to the di-axial *trans*-bromohydrin (LXI). The only possible competitor would be a transition state

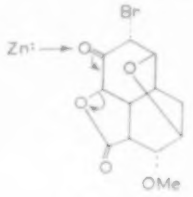
related to a bromohydrin (LXII), in which Ring D is converted to a boat conformation. In addition to the usual factors which render boat-like species energetically unfavorable relative to alternative chair forms, it may be noted that in the case at



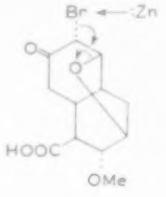
LXII

hand, the methine hydrogen atom at C.2 would offer special obstruction to the processes necessary for the formation of (LXII).

The bromohydrin (LIX) was smoothly oxidized to the corresponding ketone (LXIII) by means of chromic acid in acetic acid. We now hoped that the attack of

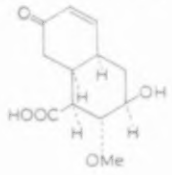


LXIII



LXIV

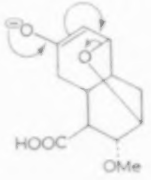
a metallic reducing agent upon (LXIII) would bring about reductive cleavage of the carbon-oxygen bond at C.8 (cf. LXIII, arrows),* as well as removal of the bromine atom and elimination of the 3,5 ether bridge (cf. LXIV, arrows),† with formation of the unsaturated keto acid (LXV). In the event, when the bromo ketone was treated



LXV

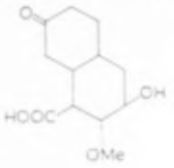
* The process involved here is of course very similar to that involved in the reductive cleavage of our γ-oxygenated α,β-unsaturated ketones (cf. footnote p. 10).

† This reaction may be direct, as implied in (LXIV), but it could well involve prior reduction of the α-bromine atom, followed by elimination of the ether bridge in the resulting enolate (xiii).



xiii

for a very short time with zinc in aqueous acetic acid, acidic products were obtained, whose ultraviolet absorption indicated clearly that the desired unsaturated ketone was present, but it was also apparent from the intensity of the absorption that substantial



LXVI

over-reduction to the saturated keto acid (LXVI) had occurred. On the other hand, when zinc and glacial acetic acid was used, the desired unsaturated keto acid was formed very smoothly.*,†

* We attribute the marked difference between the results obtained with glacial and aqueous acetic acid to the possibility that the processes leading to (LXV) utilize only zinc metal, while the reduction of (LXV) to (LXVI) involves nascent hydrogen, generated from the action of acetic acid upon zinc. It is a fact that glacial acetic acid attacks zinc very much less rapidly than the wet acid.

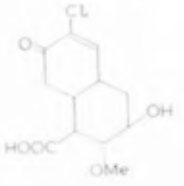
The use of other solvents than acetic acid was not successful, probably because the acid is needed to keep the zinc surface fresh, by dissolution of zinc salts formed as reaction proceeds. When the reaction was attempted in dioxane solution, containing small amounts of acetic acid and water, and the resulting acidic material was allowed to stand for some time in sodium carbonate solution, a substance of the probable structure (xvi) was formed. This compound may have resulted from reductive cleavage of (LXIII) to (xiv), followed by hydrolytic rearrangement of the α-bromine atom (xiv → xv)[12] and elimination of the 3,5 oxide bridge.

xiv

xv

xvi

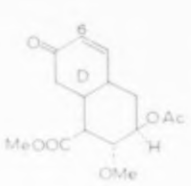
† In another series of experiments, the *chloro*hydrin corresponding to (LIX) was prepared from (LIII) by the action of hot aqueous hypochlorous acid, oxidized to the corresponding ketone, and reduced with zinc and acetic acid. The series offered no advantage, and the only point of special interest which emerged was that a by-product of zinc reduction was obtained, whose properties showed that it possessed the structure (xvii).



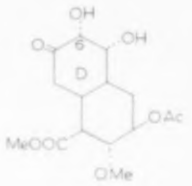
xvii

[12] L. F. Fieser and M. A. Romero *J. Amer. Chem. Soc.* **75**, 4717 (1953).

With the obtention of (LXV) our primary objective of preparing an intermediate of the general type (III) was completed. After conversion of the unsaturated keto acid to (LXVII) by esterification and acetylation, we were ready to effect cleavage of Ring D, with the ejection of C.6. Although ring cleavage could no doubt have been



LXVII



LXVIII

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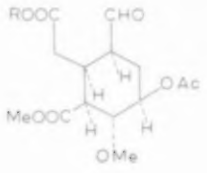
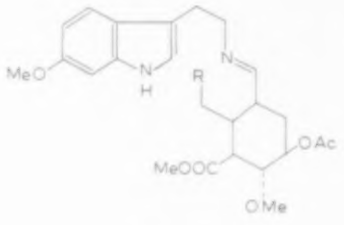
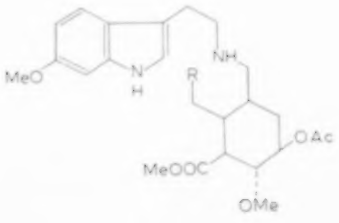
brought about directly through the use of one of a number of oxidizing agents, we chose to proceed with circumspection, and converted the unsaturated ketone first into the diol (LXVIII), through reaction with aqueous osmium tetroxide, followed



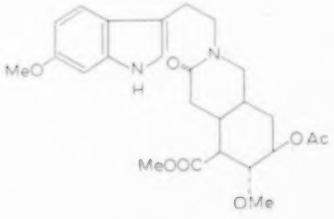
LXIX



LXX



LXXI

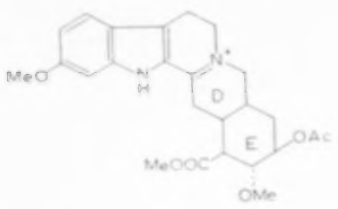


LXXII

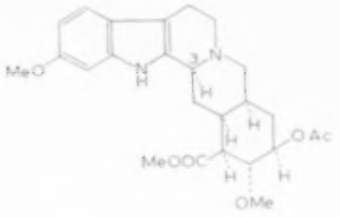
by decomposition of the intermediary osmate ester with sodium chlorate. The diol was then transformed directly in high yield, without isolation of the labile intermediates (LXIX : R = H),* (LXIX : R = Me), (LXX : R = COOMe), and (LXXI : R = COOMe), to the lactam (LXXII), through successive treatments with aqueous

* It may be noted that the aldehyde group is adjacent to an asymmetric center, but is equatorial, and consequently configurationally stable.

periodic acid and ethereal diazomethane, condensation* with 6-methoxytryptamine† in benzene, and reduction with sodium borohydride in methanol. When the lactam



LXXIII



LXXIV

was treated with boiling phosphorus oxychloride, it was smoothly converted into the quaternary cation (LXXIII), which was reduced directly with aqueous methanolic

* Infrared spectrophotometric studies of this smooth, rapid, spontaneous condensation demonstrated that the Schiff base (LXX), and simpler analogs, which were easily detectable by their weak, sharp absorption band at 6·0 μ, disappeared slowly from the solution, *particularly in the presence of excess aldehyde*. That the further reaction did not involve cyclization to the free α position of the indole nucleus was shown by the fact that precisely similar phenomena were observed in the condensation of the substituted tryptamine derivative (xviii) with aldehydes. Quite possibly the secondary reaction involves addition of the α-carbon atom of the aldehyde to the carbon-nitrogen double bond (xix → xx).

xviii xix xx

† 6-Methoxytryptamine has been prepared previously by Akabori and Saito.[13] We have prepared the base by a new synthesis: 2-Nitroanisidine (xxi) was diazotized and converted by treatment with formaldoxime to 2-nitroanisaldoxime (xxii). The corresponding aldehyde, obtained from (xxii) by steam distillation

xxi xxii

from acid solution, was condensed with nitromethane, and the resulting ω-nitrostyrene (xxiii) was reduced,

xxiii xxiv xxv

by hydrogen in the presence of palladized charcoal, to 6-methoxyindole (xxiv). Condensation of the latter with oxalyl chloride[14] gave (xxv : R = Cl), which was converted by aqueous ammonia to the amide (xxv : R = NH_2), and reduced to the desired 6-methoxytryptamine by lithium aluminium hydride in boiling tetrahydrofuran.

[13] S. Akabori and K. Saito *Ber. Dtsch. Chem. Ges.* **63**, 2245 (1930).
[14] *Cf.* M. E. Specter and W. C. Anthony *J. Amer. Chem. Soc.* **76**, 6208 (1954).

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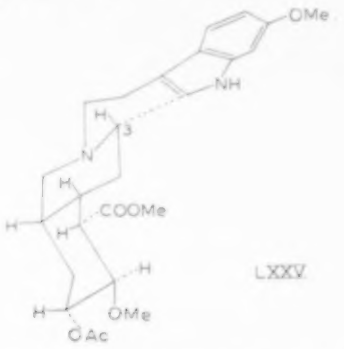
sodium borohydride to *dl* methyl-O-acetyl-*iso*reserpate (LXXIV).* It will be noted that that product is the expected one, whether the stereochemical sense of the reaction is subject to steric or thermodynamic control. Thus, attack at the convex face of the D/E ring system will place the newly added hydrogen atom at C.3 on the same side of the molecule as the bridgehead hydrogen atoms. Further, of the two possible isomers which might be formed on the creation of a new asymmetric center at C.3, (LXXIV) is the one in which all of the large groups attached to the D/E ring skeleton are equatorially disposed (cf. LXXV).



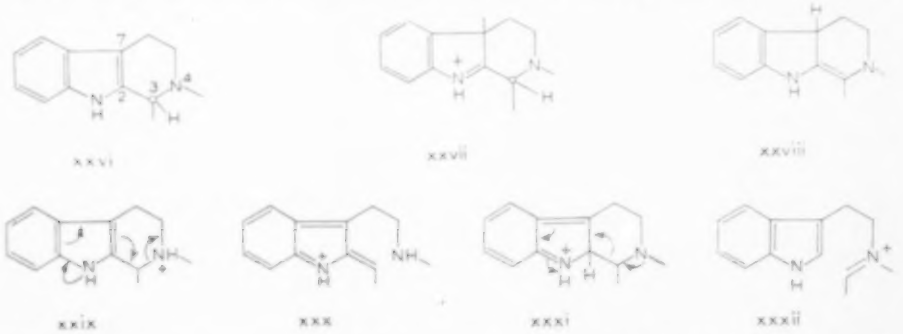
LXXV

Only one major task now remained—to effect inversion at the newly created asymmetric center, C.3. It was well known that a reaction path was available for isomerization at a center so located, through treatment with acid,† but it was clear

* We were first able to ascertain that the synthetic ester in fact possessed the structure (LXXIV) through comparison of its infrared spectrum with that of a sample of *l* methyl-O-acetyl-*iso*reserpate, prepared from reserpine.[15] Further, the racemic ester was readily resolved, using di-*p*-toluyl *l* tartaric acid, and the resulting synthetic *laevo*rotatory ester was found to be identical in all respects with material from natural sources.

The availability of *l* methyl-O-acetyl-*iso*reserpate from natural sources was also of much value in that it permitted us to pilot the experiments described in the sequel with relatively accessible optically active intermediates, at a time when the corresponding racemic synthetic compounds were in short supply.

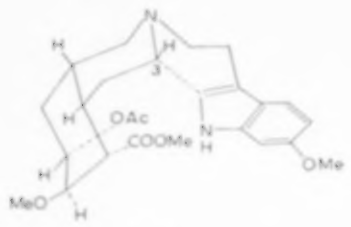
† The fact that inversions at C.3 in tetrahydrocarbolines (xxvi) can be brought about by vigorous treatment with acids is well established, though the mechanism of the changes involved is not clear. One possibility is that the indole ring is reversibly protonated at C.7, and that the resulting cation is reversibly deprotonated at C.3 (xxvi ⇌ xxvii ⇌ xxviii). Alternatively, Wenkert and Liu[4b] have suggested the reversible change



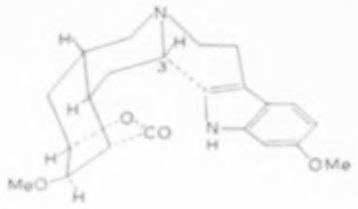
(xxix ⇌ xxx). Still another possibility lies in protonation at C.2, to give (xxxi), followed by reversible ring cleavage to (xxxii).

[15] H. B. MacPhillamy, C. F. Huebner, E. Schlittler, A. F. St. André and P. R. Ulshafer *J. Amer. Chem. Soc.* **77**, 4335 (1955).

that it would not be operative in the case at hand, since C.3 in (LXXIV ≡ LXXV) is configurationally stable. However, if the molecular framework of (LXXV) could be forced to assume the alternative conformation (LXXVI), available to it in virtue of

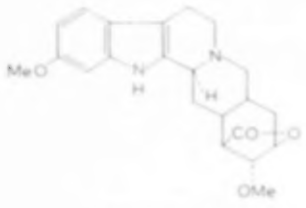


LXXVI

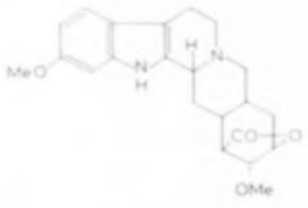


LXXVII

the *cis* locking of Rings D and E, the large indole group at C.3 would be axial, and that center should then be susceptible to inversion. Our experience with our bicyclic intermediates was clearly suggestive of the manner in which such a conformational change to a normally unfavorable state could be brought about, and we set about to prepare the lactone (LXXVII) of *iso*reserpic acid. The ester (LXXIV) was

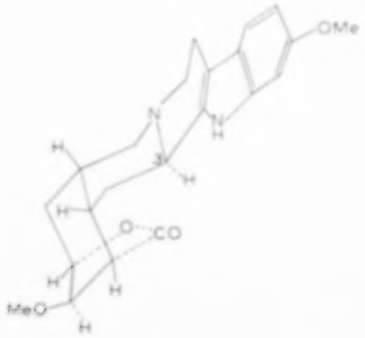


LXXVIII



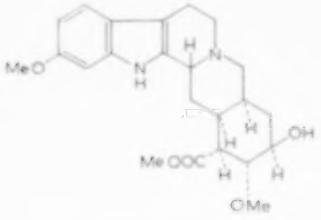
LXXIX

hydrolyzed with methanolic potash, and the resulting hydroxy acid was converted to the desired *dl isoreserpic* acid lactone (LXXVII ≡ LXXVIII) by treatment with N,N'-*dicyclo*hexylcarbodiimide in pyridine, or less efficiently by a single molar proportion of acetic anhydride in hot xylene. Further, as expected on the basis of the argument set out above, the lactone (LXXVIII) was substantially quantitatively

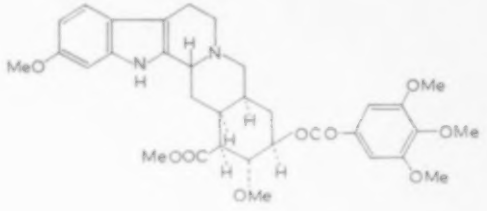


LXXX

isomerized by pivalic acid* in boiling xylene to *dl* reserpic acid lactone (LXXIX ≡ LXXX). Following known reactions[3b] in the natural series, the latter was converted by methanolysis to *dl* methyl reserpate (LXXXI), and thence, by treatment with 3,4,5-trimethoxybenzoyl chloride in pyridine, to *dl* reserpine (LXXXII ≡ II).



LXXXI



LXXXII

The racemic reserpine thus obtained was readily resolved by taking advantage of the high crystallinity and low solubility, in methanol, of *l* reserpine *d* camphor-10-sulfonate. The infrared and ultraviolet spectra of the synthetic *l* reserpine were identical in all respects with those of the natural alkaloid. Other properties of the synthetic and natural bases are summarized in Table 1.

TABLE 1

	M.p. (vac.)	$[\alpha]_D^{27°}$ ($CHCl_3$, $c = 1{\cdot}08$)
dl reserpine	260·0–262·0° (*dec.*)	
l reserpine (synthetic)	286·5–288·5° (*dec.*)*	− 120°
l reserpine (natural)	284·0–285·0° (*dec.*)*	− 118°

* Mixture m.p. 285·5–286·5° (*dec.*)

EXPERIMENTAL

Melting points, unless otherwise stated, were determined on a micro hot-stage. Those marked "(vac.)" were taken in evacuated Pyrex capillary tubes; the melting points observed for reserpine, and many related substances, are higher, sharper, and more reproducible, when observed *in vacuo*, than when taken on the hot-stage, or in open-ended capillaries. Ultraviolet spectra were measured in ethanol solution.

Infrared measurements were used for control purposes throughout this investigation, and spectra of all pure substances prepared were determined. Spectra are ordinarily recorded here only for substances in the main line of the synthesis. In each case, the abscissa is plotted in *wave lengths* (2–12 μ), and the ordinate in *percentage transmission* (0–100 per cent). For other substances, pertinent features of the spectra are described textually where desirable.

* Acetic acid, and occasionally mineral acids, have ordinarily been used in bringing about similar isomerizations. We chose pivalic acid, first in order to have a catalyst with boiling point close to that of our solvent, but mainly to suppress side reactions involving cleavage at N^b (→ —$\dot{N}$—COR) and opening of the lactone ring (→ —O—COR). All such reactions involve reaction at the carbonyl group of the acid catalyst, and will be relatively difficult with the highly hindered carbonyl function of pivalic acid.

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Synthesis of 6-methoxytryptamine

2-Nitroanisaldehyde. The following solution of formaldoxime (10 per cent) was prepared. Paraformaldehyde (69 g) and hydroxylamine hydrochloride (158 g) were heated with water (1020 cm^3) until a clear solution was obtained. Sodium acetate (306 g) was then added, and the reaction mixture was kept under gentle reflux for 15–20 min. The solution was cooled to 10° and 6 g of sodium sulfate, 37·5 g of copper sulfate and a solution of 990 g of sodium acetate in 1080 cm^3 of water were added. To this solution of formaldoxime, in a 12 l. three-necked flask, was added an ice-cold solution of 2-nitro-4-methoxybenzene diazonium chloride which had been prepared in advance, as follows. 2-Nitroanisidine (252 g) was suspended with stirring in a mixture of concentrated hydrochloric acid (342 cm^3), water (300 cm^3), and ice (600 g). A solution of sodium nitrite (105 g) in water (150 cm^3) was added slowly at 0–5°. The dark-red solution was filtered through glass wool, and a solution of sodium acetate (185 g) in water (310 cm^3) was added until the mixture was neutral to Congo paper. This solution of 2-nitro-4-methoxybenzene diazonium chloride was added below the surface of the formaldoxime solution, with vigorous stirring. The oxime of 2-nitroanisaldehyde was precipitated as a dark-brown tar which slowly coalesced into one large lump. The nitrogen liberated during the reaction tended to cause heavy foaming. Stirring was continued for 1 hr after the addition was complete. The mixture was then acidified to Congo with concentrated hydrochloric acid. The supernatant liquor was decanted from the tarry oxime, to which ferric ammonium sulfate (1800 g) and water (3 l.) were added. This mixture was heated under reflux for 40 min, and then distilled with steam. The 2-nitroanisaldehyde separated from the distillate on cooling. The first fraction of distillate usually contained a considerable amount of *m*-nitroanisol (orange-yellow, m.p. 38°), which was separated from the desired aldehyde via bisulfite treatment. The steam distillation was continued until no more aldehyde separated from the distillate. The aldehyde was then collected, washed with water, and dried. One hundred and seventy grams of 2-nitroanisaldehyde, m.p. 95–96°, were obtained. For analysis the aldehyde was recrystallized four times from chloroform/petroleum ether, m.p. 95·5–96°.

Anal. Calcd. for $C_8H_7O_4N$: C, 53·04; H, 3·90; N, 7·73. Found: C, 53·30; H, 4·19; N, 7·68.

The 2,4-*dinitrophenylhydrazone*, crystallized once from glacial acetic acid/ethanol (2 : 1) and three times from nitrobenzene, melted at 222–223°.

Anal. Calcd. for $C_{14}H_{11}O_7N$: C, 46·54; H, 3·07; N, 19·39. Found: C, 46·80; H, 3·08; N, 19·63.

2,β-Dinitro-4-methoxystyrene. A mixture of 2-nitroanisaldehyde (10 g), nitromethane (10 cm^3), ammonium acetate (4 g) and glacial acetic acid (40 cm^3) was heated under reflux in an atmosphere of nitrogen for 2 hr. The hot dark-red solution was slowly poured into 200 cm^3 of ice water with vigorous stirring. The styrene was precipitated as an oily brown material which slowly solidified. The mixture was stirred for 3 hr and then filtered. When the filter cake was washed well with water and dried *in vacuo*, 11 g of amorphous brown crude styrene were obtained. The material was dissolved in chloroform, washed once with saturated sodium bisulfite solution, twice with saturated brine, and dried over anhydrous sodium sulfate. It was then heated under reflux for a few minutes with Norite and filtered through Celite. The filtrate was concentrated to a small volume and petroleum ether was

added to bring about crystallization of the product. After 2 hr at room temperature, 8 g of 2,β-dinitro-4-methoxystyrene, m.p. 103°, was collected. For analysis the substance was recrystallized four times from chloroform/petroleum ether, appearing as beautiful long yellow needles, m. p. 103–104°.

Anal. Calcd. for $C_9H_8O_5N_2$: C, 48·22; H, 3·60; N, 12·50. Found: C, 48·30; H, 3·59; N, 12·53.

6-*Methoxyindole.* 2,β-Dinitro-4-methoxystyrene (25 g) was dissolved in ethyl acetate (281 cm³). To this solution, 31 cm³ of ethanol, 35 cm³ of glacial acetic acid and 2·5 g of palladium/charcoal(10 per cent) were added. The mixture was reduced with hydrogen under a pressure of 50 lb/in². The consumption of hydrogen was very rapid, and the reaction strongly exothermic. When the reduction was complete, the mixture was filtered through Celite. The filtrate was added with stirring to a mixture of ether and saturated sodium bicarbonate solution. The two phases were separated, and the ether phase was extracted several times with water to remove ethanol, acetic acid and ammonium acetate. The ether solution was then dried over anhydrous sodium carbonate, and concentrated to approximately 30 cm³. When petroleum ether was added to the concentrate, crude 6-methoxyindole was precipitated as a brown crystalline mass which was collected after 2 hr (11 g). The crude indole was dissolved in ether, and the ethereal solution was filtered through a column of 75 g of basic aluminium oxide (Merck, activity I). The filtrate was concentrated to a very small volume and petroleum ether was added. Pure, almost colorless 6-methoxyindole (9 g), m.p. 91°, crystallized readily. For analysis the substance was recrystallized three times from petroleum ether, m.p. 91–92°.

Anal. Calcd. for C_9H_9ON: C, 73·45; H, 6·16; N, 9·52. Found: C, 73·53; H, 6·34; N, 9·51.

Ultraviolet spectrum: $\lambda\lambda_{max}$ 220 mμ (ε 29,100), 267 mμ (ε 4100), 292 mμ (ε 5370).

β-6-*Methoxyindolyl-glyoxylic acid chloride.* 6-Methoxyindole (20 g) was dissolved in anhydrous ether (400 cm³) with shaking. Oxalyl chloride (20 cm³) was gradually added at 0°. The bright-red product crystallized readily. After 30 min at 0°, it was collected and washed liberally with ether. Twenty-nine grams (90 per cent) of the chloride, m.p. 125–128° (dec.) → 150–165°, were obtained.

Anal. Calcd. for $C_{11}H_8O_3NCl$: Cl, 14·90. Found: Cl, 14·36.

β-6-*Methoxyindolyl-glyoxylic acid amide.* β-6-Methoxyindolyl-glyoxylic acid chloride (29 g) was added gradually with vigorous stirring to 500 cm³ of concentrated aqueous ammonia. Reaction took place instantaneously with formation of the yellow amide. After the addition was complete, stirring was continued for 30 min at 40–50°. The mixture was then cooled to 10–20°, and the product was collected (24 g, 90 per cent). For analysis the amide was crystallized four times from tetrahydrofuran/ether m.p. 258–259°.

Anal. Calcd. for $C_{11}H_{10}O_3N_2$: C, 60·54; H, 4·62; N, 12·84. Found: C, 60·54; H, 4·66; N, 12·82.

6-*Methoxytryptamine.* β-6-Methoxyindolyl-glyoxylic acid amide (20 g), dried in high vacuum, was dissolved in 600 cm³ of anhydrous tetrahydrofuran under gentle reflux in a 3 l. three-necked flask equipped with stirrer, reflux condenser, and dropping funnel. The entire reaction was carried out in an atmosphere of nitrogen. To the solution of the amide, fresh lithium aluminium hydride (20 g) slurried in 400 cm³ of anhydrous tetrahydrofuran was added carefully in small portions. The orange-red

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mixture was kept under gentle reflux overnight. The reaction vessel was then cooled in ice, and 1 kg of methylene chloride was added. Excess lithium aluminium hydride was destroyed with wet tetrahydrofuran. Water was then added until the precipitated hydroxides formed large lumps. The mixture was filtered through Celite and the filter cake was washed with 1 kg of methylene chloride. The filtrate was extracted with a total of 1·41 of 10 per cent aqueous acetic acid, in four portions. The acetic acid extract was concentrated somewhat *in vacuo* to remove organic solvents. It was then refluxed for 5 min with Norite, under nitrogen, filtered through Celite directly onto ice, made alkaline with sodium hydroxide, and extracted several times with methylene chloride. The methylene chloride extract was washed twice with saturated brine and dried over anhydrous potassium carbonate. When the solvent was removed, 11 g (63 per cent) of crude crystalline 6-methoxytryptamine were obtained. For purification, the base was dissolved in a small amount of methanol and brought to boil. The boiling methanol was then gradually displaced by hot benzene. When the mixture was cooled, the pure 6-methoxytryptamine crystallized in beautiful silky, almost colorless, needles, m.p. 142°. For analysis the base was crystallized three times from aqueous methanol, m.p. 140–141°.

Anal. Calcd. for $C_{11}H_{14}ON_2$: C, 69·44; H, 7·42; N, 14·73. Found: C, 69·24; H, 7·56; N, 14·80.

Ultraviolet spectrum: $\lambda\lambda_{max}$ 224 mμ (ε 33,300), 274 mμ (ε 4620), 293 mμ (ε 5580).

The corresponding *hydrochloride*, twice crystallized from ethanol/ether, melted at 221–223°.

Anal. Calcd. for $C_{11}H_{14}ON_2 \cdot HCl$: C, 58·27; H, 6·67; N, 12·35; Cl, 15·64. Found: C, 58·27; H, 6·91; N, 12·32; Cl, 15·47.

Preparation and characterization of the adducts (IV)

Cis-5, 8-*diketo*-1,4,5,8,9,10-*hexahydronaphthalene*-1-*carboxylic acid* (IV: R = H). Vinylacrylic acid is a sensitive substance, whose isolation in a pure state is attended by severe losses. Further, the pure acid cannot be kept more than a short time before serious decomposition sets in. In these circumstances, we found it convenient to use a freshly prepared crude solution of vinylacrylic acid for the addition reaction with quinone. It should be mentioned, however, that reactions on a small scale, using pure, isolated, vinylacrylic acid, gave the adduct (IV) in yields comparable with or rather better than that described below. The following procedure for the preparation of the vinylacrylic acid solution is patterned after that of Kohler and Butler.[16]

The condensation of malonic acid with acrolein was carried out in three identical separate batches. In each, 2000 g of malonic acid were added to 4·5 l. of pyridine (technical, containing 0·5 per cent of water) with vigorous stirring. After about 40 min the major part of the malonic acid had dissolved. The mixture was then cooled to 10° in an ice-cold bath, and 1333 g of acrolein were added at such a rate that the temperature did not exceed 12°. The addition was complete in about 90 min; stirring was then continued for 3 hr at 0° and subsequently for 5 hr at 35–40°. (The reaction mixture is very viscous at 0° and becomes fairly mobile at 35–40°.) At the end of the stirring period, the three batches were combined and slowly added to 13 l. of a 50

[16] E. P. Kohler and F. R. Butler *J. Amer. Chem. Soc.* **48**, 1041 (1926). Cf. also O. Doebner *Ber. Dtsch. Chem. Ges.* **35**, 1137 (1902); K. Alder and W. Vogt *Liebigs Ann.* **570**, 196 (1950).

per cent (v/v) aqueous solution of sulfuric acid at −5°, with stirring, and at such a rate that the temperature did not exceed 15–20°. The mixture, which was acidic to Congo, was filtered through Celite. The clear yellow filtrate was extracted six times with ether (three times with 7 gal and three times with 3 gal each). The ether extracts were twice washed quickly with water, dried over anhydrous sodium sulfate, and concentrated to 3 gal. Six gallons of benzene were then added, and the mixture was again concentrated to 3 gal.

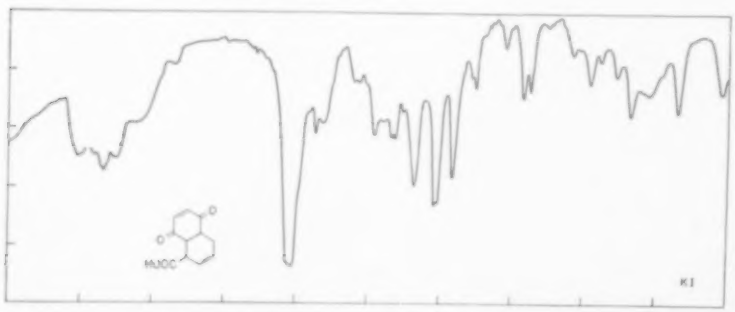
Three and one-half kilograms of quinone (Eastman Kodak Practical, recrystallized by Soxhlet extraction with octane; if large crystals of quinone are present, the material should be ground before use), dissolved in 2 gal of benzene, were added to the above benzene solution of vinylacrylic acid. The mixture was heated under reflux for 3 hr, and then filtered hot (*c.* 45–50°). The filter cake comprised 2·3 kg of grey crude adduct. The benzene mother liquors were concentrated at normal pressure to *c.* 1·5 gal and again filtered hot. This second filtration gave a further 700 g of adduct, black in color. The filtrate was discarded. The combined fractions of crude adduct (3 kg) were dissolved under reflux in a mixture of 30 l. of pure acetone and 30 l. of pure methanol. Norite (450 g) was added to the clear, dark-red, solution, and the mixture was kept under reflux for 10 min. It was then filtered hot and under pressure through a large-diameter filter, pre-coated with Celite. During filtration, the solution was kept at about 50°. The filtrate was cooled to 10–15°, and 70 l. of pentane were added gradually, with stirring. The adduct crystallized readily in almost colorless small prisms. The mixture was stirred at 10–15° for 3 hr and then filtered. The filter cake was washed with acetone/pentane (1 : 2) until it did not darken on exposure to air. The product was then washed with pentane, and air dried. Yield: 2 kg, m.p. 215–225°.

The adduct could be recrystallized readily by addition of pentane to its solutions in acetone, ethyl acetate, chloroform, or acetone/methanol mixtures, or from tetrahydrofuran/ether. After two crystallizations from the latter solvent, the air-dried material had m.p. 223–229°. Although no sharp-melting sample of the adduct was ever obtained, a fourteen-plate counter-current distribution of once-crystallized material, m.p. 215–225°, using 70 per cent aqueous methanol versus chloroform/ethyl acetate (1 : 18) revealed no significant amount of any contaminating substance.

For analysis the adduct was twice crystallized from water, m.p. 215–225°.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64·07; H, 4·89. Found: C, 63·91: H, 5·00

Ultraviolet spectrum: λ_{max} 224 mμ (ε 11,300) and 355 mμ (ε 71).



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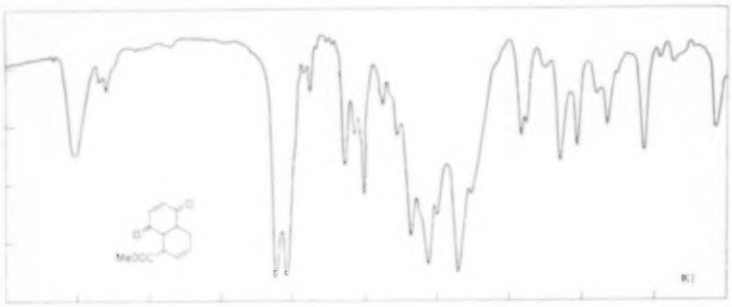
The *methyl ester* (IV : R = H) was prepared either by methylation of the acid adduct (IV : R = H) with diazomethane, or by reaction of quinone with methyl vinylacrylate. Neither of these methods was investigated extensively with a view to determining optimum conditions.

Method (a). Two grams of the adduct (IV : R = H) were dissolved in 50 cm^3 of methylcellosolve and treated on 0–5° with 1·2 moles of ethereal diazomethane solution. The reaction mixture was allowed to stand for 15 min at 0° and then for 2 hr at room temperature. It was then evaporated to dryness *in vacuo*. When the residue was extracted several times with boiling ether, 300 mg of crystalline starting material remained undissolved. The combined ethereal extracts were shaken with ice-cold sodium bicarbonate solution, dried with sodium sulfate, and taken to dryness *in vacuo*. When the residue was crystallized from ether, 910 mg of thick glassy prisms of the desired ester, m.p. 103–104°, were obtained. For analysis this material was dried for 5 hr at 60° in high vacuum.

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65·44; H, 5·59. Found: C, 65·07; H, 5·57.

Ultraviolet spectrum: λ_{max} 223 mμ (ε 10,670).



When the mother liquors from the above preparation were allowed to stand, a considerable amount of crystalline material separated. When this was washed with benzene and crystallized from methanol, it had m.p. 168–170°, and was shown to be the aromatic ester (VI) (see below).

Method (b). Methyl vinylacrylate, b.p. 57–58°/25 mm (n_D^{25} 1·4797), was prepared by esterification of crude vinylacrylic acid, obtained by evaporation of the benzene concentrate, whose preparation is described above, by boiling in methanol containing sulfuric acid for 3 hr. A sample of the ester so obtained (63 g) was heated under reflux for 10 hr with 70 g of quinone in 200 cm^3 of benzene. The reaction mixture was then shaken successively with aqueous sodium bisulfite and dilute aqueous potassium hydroxide. During the last of these separations, 34 g of a colorless solid, m.p. 120–125°, separated, which was crystallized from acetone/ether, m.p. 125–126°. This substance was shown to be a molecular compound of the desired adduct ester (IV: R = Me) with hydroquinone.

Anal. Calcd. for $C_{12}H_{12}O_4 \cdot C_6H_6O_2$: C, 65·44; H, 5·50; OMe, 9·4. Found: C, 65·24; H, 5·63; OMe, 10·58.

The ultraviolet and infrared spectra of the substance were composites of those of hydroquinone and the ester (IV: R = Me). When the material was dissolved in

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methylene chloride and shaken with ice-cold dilute aqueous potassium hydroxide, the ester (IV: R = Me) was recovered from the methylene chloride phase. This procedure for the separation of the components was attended by considerable loss, and undoubtedly does not represent the best method for recovering the desired ester from the molecular complex.

The filtrate from the separation of the molecular compound was further washed with dilute aqueous potash, then with water, dried over sodium sulfate, and evaporated. When the residue was dissolved in benzene and allowed to stand, 13 g of the aromatic ester (VI), m.p. 170–172°, separated. After removal of this material, the filtrate was concentrated *in vacuo*, dissolved in ether, and seeded with a specimen of the ester (IV: R = Me). Overnight, 10·2 g of the ester (IV: R = Me), m.p. 98–103°, separated.

5,8-*Dihydroxy*-1,4-*dihydronaphthoic acid methyl ester* (VI). The adduct (IV: R = H) (500 mg) was suspended in 4 cm³ of methanol. The reaction mixture was saturated with hydrogen chloride at 0°, and allowed to stand overnight. The solution was then taken to dryness *in vacuo*, and the residue crystallized by trituration with ether. Recrystallization from methanol/ether gave colorless needles, m.p. 168–170°.

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65·44; H, 5·50. Found: C, 65·09; H, 5·66.

Ultraviolet spectrum: λ_{max} 210 mμ (ε 7090) and λ_{max} 294 mμ (ε 3710).

The infrared spectrum ($CHCl_3$) displayed sharp phenolic hydroxyl absorption at 3·00 μ, and an ester band at 5·83 μ.

5,8-*Diketo*-1,4,5,6,7,8,9,10-*octahydronaphthoic acid.* When the adduct (IV: R = H) was reduced with zinc and acetic acid, the conjugated double bond ($\Delta^{6,7}$) was reduced. The adduct (IV: R = H) (2 g) was dissolved in a mixture of 40 cm³ of acetic acid and 20 cm³ of water. Four grams of zinc dust were added with stirring over a period of 10 min, and the stirring was continued for a further 15 min. The zinc was then removed by filtration, and the filtrate was concentrated *in vacuo* to about 4 cm³. The material which separated was dissolved in chloroform, filtered from some insoluble matter, and concentrated to dryness. Crystallization from chloroform gave 860 mg of crystalline solid, m.p. 154·5–158°. After recrystallization from acetone, the melting point was 159–160°, and was not elevated by further recrystallization.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63·45; H, 5·81. Found: C, 63·03; H, 5·95.

This compound showed no high intensity absorption in the ultraviolet above 210 mμ.

The infrared spectrum ($CHCl_3$) in the carbonyl region possessed only a single rather broad band (λ_{max} 5·85 μ).

Acetylation of the adduct (IV: R = H). The adduct (IV: R = H) (100 mg) was dissolved in 6 cm³ of a solution of acetic anhydride containing 3 per cent of acetyl chloride, and allowed to stand at room temperature for 7 hr. The reaction mixture was then taken to dryness *in vacuo* at 70°. The crystalline residue was washed thrice with cold ethanol and recrystallized three times from acetone/ethanol. Thirty-five milligrams of the *mixed anhydride* (XI) were obtained as fine colorless needles, m.p. 120–122°. For analysis, the material was dried for 6 hr at 60° in high vacuum.

Anal. Calcd. for $C_{13}H_{12}O_5$: C, 62·90; H, 4·87. Found: C, 62·79; H, 5·18.

Ultraviolet spectrum: λ_{max} 224 mμ (ε 8970).

The infrared spectrum ($CHCl_3$) possessed bands at 5·48, 5·68 and 5·90 μ.

Oxidation of the ester adduct (IV: R = Me) *by perbenzoic acid.* The ester adduct (IV: R = Me) (440 mg) was dissolved in 4 cm³ of benzene and treated with 4 cm³ of a 0·63 M solution of perbenzoic acid in benzene. After it had stood for 20 hr at room temperature, the reaction mixture was shaken successively with dilute aqueous sodium iodide, sodium thiosulfate, acetic acid, and sodium bicarbonate. It was then dried over sodium sulfate and concentrated *in vacuo*. When the residue was twice crystallized from benzene/ether, 244 mg of the *oxide* (VII), m.p. 136–139°, were obtained as colorless needles. For analysis, the substance was crystallized further from chloroform/ether (m.p. 140–141°) and dried at 60° in high vacuum for 5 hr.

Anal. Calcd. for $C_{12}H_{12}O_5$: C, 61·01; H, 5·12. Found: C, 61·06; H, 5·25.

Ultraviolet spectrum: λ_{max} 221 mμ (ε 10,380).

The infrared spectrum ($CHCl_3$) possessed bands at 5·73 and 5·90 μ.

Hydroxylation of the oxide (VII). The oxide (VII) (600 mg) was treated with 50 cm³ of a solution prepared by shaking 3 cm³ of perhydrol (30 per cent) with 100 cm³ of ether and drying with sodium sulfate. After addition of 20 cm³ of benzene to bring the oxide into solution, 50 mg of osmium tetroxide in 5 cm³ of ether were added. After standing for 37 hr at room temperature, the solution had deposited well-formed crystals which were removed by filtration and washed with ether. When the mother liquor was taken to dryness *in vacuo* and the residue triturated with acetone, further crystalline material was obtained (total, 335 mg). After three recrystallizations from acetone, the diol (VIII) was obtained as elongated colorless prisms, m.p. 159–161° (*dec.*); it was dried for analysis for several hours at 80° in high vacuum.

Anal. Calcd. for $C_{12}H_{14}O_7$: C, 53·33; H, 5·22. Found: C, 53·61; H, 5·53.

This compound showed no intense ultraviolet absorption above 210 mμ.

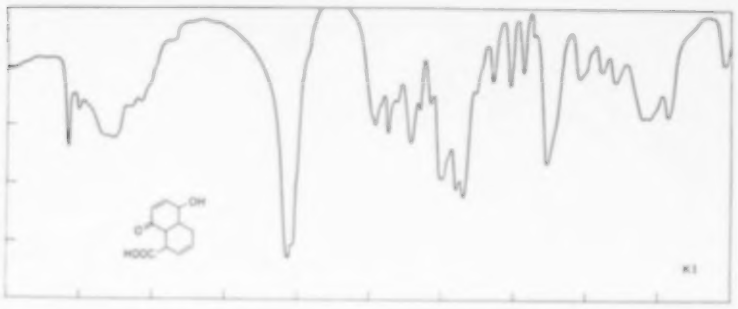
The infrared spectrum (KI) possessed bands at 2·95, 5·75 and 5·80 μ.

Preparation of the dihydro adduct (XII). *The six-membered lactone series*

Cis-5-*hydroxy*-8-*keto*-1,4,5,8,9,10-*hexahydronaphthoic acid* (XII). Three hundred grams of the adduct (IV: R = H) were slurried with 2000 cm³ of water, and cooled in an ice bath. One hundred and twenty-three grams of sodium bicarbonate dissolved in 2000 cm³ of water were then added slowly. A thin layer of ethyl acetate was maintained on top of the reaction mixture to prevent foaming. When nearly all of the adduct had dissolved, 35 g of sodium borohydride, dissolved in water, were added in portions, and the mixture was then stirred for 15 min. Ethyl acetate (1000 cm³) was then added, and the solution was acidified to Congo with 20 per cent aqueous sulfuric acid. The acidic solution was seeded with a sample of the dihydro derivative (XII) and stirred at 0° for another 30 min. The product which separated was removed and washed with *c.* 2000 cm³ of water. After having been dried, this crude material weighed 220 g. Ethyl acetate (500 cm³) was then added to the mother liquors, and the two phases were separated. The dark-colored organic phase was discarded, and the remaining aqueous liquor was extracted three times with ethyl acetate. The combined extracts were washed twice with saturated sodium chloride solution, and dried over anhydrous sodium sulfate. When the extract was concentrated and treated with ether, a further 20 g of the dihydro adduct separated. Total yield: 240 g (80 per cent). For analysis the dihydro derivative was crystallized three times from aqueous methanol, m.p. 179–180°.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63·45; H, 5·81. Found: C, 63·47; H, 6·08.

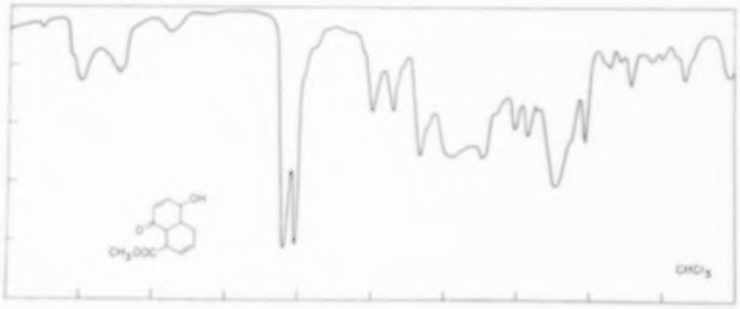
The ultraviolet spectrum of (XII) showed only end absorption ($\varepsilon_{215m\mu}$ 5000).



The corresponding *methyl ester* (XXXVII) was prepared by the action of diazomethane upon (XII). The latter (5 g) was dissolved in 50 cm³ of anhydrous dioxane. One mole of diazomethane in ether was added at 0°, and the solvents were removed *in vacuo*; the temperature was not allowed to rise above 30°. When only a small amount of dioxane was left, ether was added, and 3·5 g of the ester (XXXVII) crystallized readily on scratching. For analysis the ester was recrystallized four times from acetone/ether, m.p. 93–94°.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64·85; H, 6·35. Found: C, 64·57; H, 6·48.

Ultraviolet spectrum: λ_{max} 215 mμ (ε 7200).



When attempts were made to effect esterification of (XII) with methanol in the presence of acid catalysts, even under very mild conditions, non-crystalline products were obtained, whose ultraviolet spectra indicated clearly that aromatization had occurred to a considerable extent.

Cis-5-*hydroxy*-8-*ketodecahydronaphthoic acid* (XIV). The dihydro derivative (XII) (5 g), dissolved in 250 cm³ of glacial acetic acid, was shaken under hydrogen in the presence of 0·25 g of pre-reduced palladium-barium sulfate catalyst. In 2 hr 2 moles of hydrogen had been absorbed, and the consumption of hydrogen had ceased. When the residue, after removal of catalyst and solvent, was crystallized from ethyl acetate/ether, 4·7 g of crystalline hydroxy acid (XIV), m.p. 147–149°, were obtained. The analytical sample, obtained by crystallization from acetone/ether, had m.p. 153–155°.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62·25; H, 7·60. Found: C, 62·08; H, 7·54.

No high intensity ultraviolet absorption above 210 mμ was observed.

The corresponding *methyl ester* was obtained by treatment of (XIV) with diazomethane. The ketohydroxy acid (XIV) (4·5 g) was dissolved in 200 cm³ of absolute

dioxane. The solution was cooled to 15°, and 60 cm³ of ethereal 1·9 per cent diazomethane solution were added. The solvent was then removed *in vacuo* at 40°. When the residual oil was crystallized from ether acetate/ether, 4·2 g of the ester, m.p. 115–118°, were obtained. Further crystallization from acetone/ether raised the melting point to 125–126°. This substance was converted into an *acetyl derivative*. The ester (4 g) was dissolved in absolute pyridine (20 cm³) and acetic anhydride (15 cm³). The reaction mixture was allowed to stand at room temperature for 15 hr, and then concentrated to dryness *in vacuo*. The residue was dissolved in chloroform/ether (1 : 3) and washed twice with 2 N hydrochloric acid, twice with aqueous sodium bicarbonate and finally with saturated sodium chloride solution. The dried solvent was evaporated *in vacuo*, and the residue crystallized from ethyl acetate/ether. The *acetyl derivative* (4 g, 85 per cent), was obtained as colorless prisms, m.p. 128–129°, raised to 129–130° by further crystallization from acetone/ether.

Anal. Calcd. for $C_{14}H_{20}O_5$: C, 62·67; H, 7·51. Found: C, 62·93; H, 7·49.

The saturated lactone (XV). The hexahydro derivative (XIV) (1 g), sodium acetate (0·2 g), acetic anhydride (1 cm³) and benzene (20 cm³) were heated under reflux in an atmosphere of nitrogen for 2 hr. The cooled solution was taken up in chloroform, washed twice with saturated sodium bicarbonate, and then with water. After the extract had been dried over sodium sulfate and evaporated, the residue was crystallized from acetone/ether: 585 mg (64 per cent), m.p. 123–125°. For analysis the lactone was recrystallized from acetone/ether, m.p. 127–128°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68·02; H, 7·27. Found: C, 67·41; H, 6·95.

The infrared spectrum of the saturated lactone in chloroform solution possessed a complex, not quite completely resolved, band in the carbonyl region. A potassium iodide spectrum, however, showed two clearly resolved bands at 5·80 and 5·85 μ.

The 2,4-*dinitrophenylhydrazone* of the saturated lactone, crystallized from dichloromethane/methanol, had m.p. 246–248°. Its infrared spectrum possessed a single sharp band in the carbonyl region, at 5·79 μ.

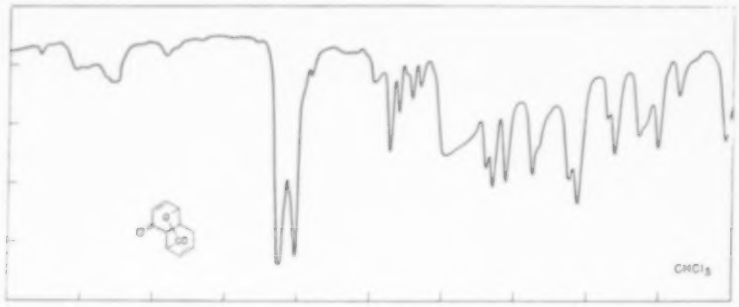
An alternative method of preparing the saturated keto lactone (XV) is described below.

Preparation of the transannular six-membered lactone (XIII). A mixture of 200 g of the dihydro derivative (XII), 200 cm³ of acetic anhydride, 40 g of anhydrous sodium acetate, and 4000 cm³ of benzene was heated under reflux with vigorous stirring. The insoluble dihydro derivative dissolved slowly; in about 15 min the reaction mixture was a clear yellow solution containing some undissolved sodium acetate. After the mixture had been heated for 1 hr, it was cooled in an ice bath, and 2000 cm³ of ethyl acetate and some ice-cold water were added with stirring. The phases were separated, and the organic phase was extracted once with ice-cold sodium bicarbonate. The combined aqueous phases were back-washed with ethyl acetate. The ethyl acetate solutions were combined, washed twice with saturated sodium chloride solution, and dried over sodium sulfate. When the solvent was concentrated to a small volume, crystallization of the lactone (XIII) commenced. Ether was added, and the mixture was kept in the cold for a few hours. The crystalline product was cooled and washed well with ethyl acetate/ether, and subsequently with ether alone: 111 g. From the mother liquors, another 10 g of the lactone were recovered. Total yield: 121 g (66 per cent). For analysis, the lactone was crystallized once from acetone.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69·46; H, 5·30. Found: C, 69·41; H, 5·29.

Ultraviolet spectrum: λ_{max} 220 mμ (ε 9200).

The infrared spectrum of the lactone in chloroform solution possessed bands at 5·74 and 5·96 μ.



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Hydrogenation of (XIII) gave the saturated lactone (XV), whose preparation by an alternative method is described above. The keto lactone (XIII) (1·27 g) dissolved in dry dioxane (20 cm^3) was shaken under hydrogen in the presence of a pre-reduced palladium-barium sulfate catalyst (300 mg). In 2 hr 30 min 2 moles of hydrogen had been absorbed and the absorption ceased. The residue, after removal of catalyst, and concentration *in vacuo*, was crystallized from ether, and gave 1·05 g (82 per cent) of the saturated keto lactone (XV), m.p. 126–127°, identical with the material described above.

Bromination of the unsaturated keto lactone (XIII). The lactone (XIII) (190 mg) was dissolved in 5 cm^3 of glacial acetic acid. A solution of bromine in acetic acid (2·9 g bromine in 25 cm^3 glacial acetic acid) was added drop-wise with cooling and stirring until the reaction mixture remained slightly yellow. The excess of bromine was destroyed with a few drops of 1 N sodium thiosulfate solution, and the solvent was evaporated *in vacuo* at 40°. The residual oil was dissolved in ethyl acetate and the organic layer was washed with saturated sodium bicarbonate and water. The dried extract was evaporated *in vacuo* at 40°, and the residue crystallized from ether. The bromolactone (i) (268 mg) was obtained as colorless prisms, m.p. 156–162°. For analysis the bromo derivative was recrystallized from acetone/ether, m.p. 167–168°.

Anal. Calcd. for $C_{11}H_9O_3Br$: C, 49·10; H, 3·37; Br, 29·70. Found: C, 49·06; H, 3·14; Br, 29·81.

Ultraviolet spectrum: λ_{max} 253 mμ (ε 4250).

The infrared spectrum of the bromolactone in chloroform possesses bands at 5·72 and 5·91 μ. In solid potassium iodide the lower wavelength band is displaced to 5·78 μ.

Preparation of the iodoacetate (ii). To a well-stirred suspension of the unsaturated keto lactone (XIII) (3·8 g) and silver acetate (3·4 g) in glacial acetic acid (100 cm^3), finely powdered iodine (5 g) was added. After the mixture had been stirred for 2 hr 30 min, a further 100 mg of silver acetate was added to destroy excess iodine. The mixture was then filtered through Celite, and the filtrate was evaporated *in vacuo*. The residue solidified, and was recrystallized from dichloromethane to give 3·2 g

of slightly yellow *iodoacetate* (ii), m.p. 185–186° (*dec.*). For analysis the substance was recrystallized from dichloromethane/ether, and was obtained as colorless prisms, m.p. 186° (*dec.*).

Anal. Calcd. for $C_{13}H_{13}O_5I$: C, 41·40; H, 3·49; I, 33·70. Found: C, 41·02; H, 3·65; I, 33·94.

Ultraviolet spectrum: λ_{max} 222 mμ (ε 4000).

Zinc reduction of the lactone (XIII): Cis-8-*keto*-1,4,7,8,9,10-*hexahydronaphthoic acid* (viii). The lactone (XIII) (1 g) was dissolved in 10 cm³ of warm glacial acetic acid. The solution was cooled to room temperature, and 3·25 cm³ of water were added. Zinc dust (2 g) was added with vigorous stirring, and the mixture was then stirred further for 10 min. The zinc was removed by filtration, and the filter cake was washed with aqueous acetic acid of the concentration used for the reaction. The filtrate was then poured into a large amount of ethyl acetate. The ethyl acetate solution, from which considerable zinc acetate had separated, was washed twice with water and once with saturated sodium chloride solution, and then dried over sodium sulfate. When the solvent was removed *in vacuo*, the residue crystallized readily, and after recrystallization from ethyl acetate, 1 g of the keto acid (viii), m.p. 155–158°, was obtained. For analysis the acid was recrystallized three times from ethyl acetate, m.p. 154–156°.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68·73; H, 6·29. Found: C, 68·93; H, 6·47.

The corresponding *methyl ester* was formed when the keto acid (viii) (1 g) was dissolved in a small amount of methanol, and the cooled solution (5°) was treated with excess ethereal diazomethane. The ester crystallized readily after the solvents were removed *in vacuo* and ether was added. For analysis the ester was recrystallized three times from ether containing a small amount of petroleum ether, m.p. 68·5–69°.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69·88; H, 6·84. Found: C, 69·94; H, 6·98.

Ultraviolet spectrum: weak end absorption ($\varepsilon_{215m\mu}$ 506).

The infrared spectrum possessed a poorly resolved complex band in the carbonyl region, with indications of maxima at 5·78 and 5·84 μ.

The ester was transformed into a corresponding *ethylene thioketal*: The ester (1·1 g) was dissolved in glacial acetic acid (5 cm³). Ethanedithiol (0·7 cm³) and freshly distilled boron trifluoride etherate (0·7 cm³) were added, and the solution was kept at room temperature for 1 hr 45 min. The reaction mixture was then poured into a large amount of ice-cold ethyl acetate. The solution was then washed twice with ice-cold sodium bicarbonate, once with saturated sodium chloride solution, and dried over magnesium sulfate. When the solvent was removed, 1·5 g of a yellowish oil remained. This residue was filtered through a short column of neutral alumina (Woelm, activity I) in methylene chloride/benzene (1 : 1). The first two 20 cm³ fractions of the eluate gave 550 mg and 260 mg respectively of almost entirely crystalline thioketal. The first fraction was distilled in high vacuum (125–135° air-bath temperature) and subsequently recrystallized three times from ether containing a little petroleum ether, m.p. 118–118·5°.

Anal. Calcd. for $C_{14}H_{18}O_2S_2$: C, 59·54; H, 6·42; S, 22·75. Found: C, 59·42; H, 6·47; S, 23·25.

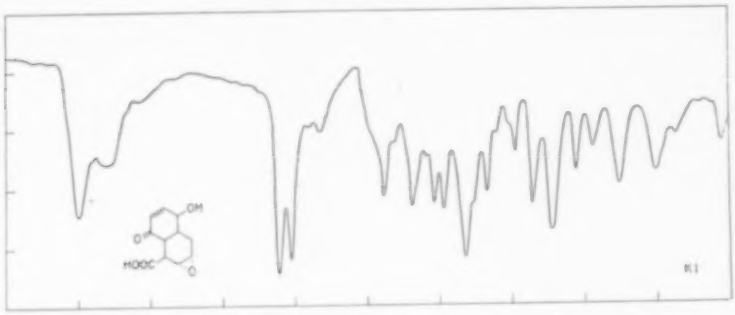
Ultraviolet spectrum: no absorption.

Perbenzoic acid oxidation of the dihydro derivative (XII): Cis-2,3-*oxido*-5-*hydroxy*-8-*keto*-1,2,3,4,5,8,9,10-*octahydronaphthoic acid* (XIX). The dihydro derivative (XII)

(35 g, 0·168 mole) was dissolved (by warming) in 300 cm³ of dioxane. To the cooled solution, 320 cm³ of 0·605 M perbenzoic acid in benzene (0·194 mole) were added. The resulting mixture, which became warm, was allowed to stand at room temperature for 25 hr. When the solvent was removed *in vacuo*, and the residue was treated with ethyl acetate, the product crystallized. After the residue had been triturated with ethyl acetate in ether, 26 g of colorless oxide, m.p. 156–160°, was collected. Concentration of the mother liquors afforded a further 4 g of product, m.p. 150–156°: the total yield of the crude oxide (XIX) was 80 per cent. For analysis the material was crystallized from ethyl acetate to give colorless prisms, m.p. 160–161°.

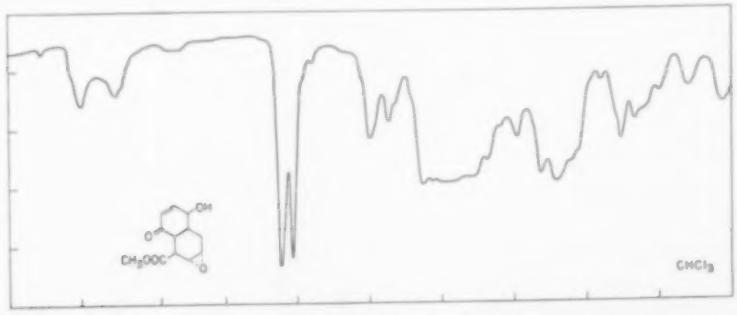
Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58·92; H, 5·40. Found: C, 58·86; H, 5·64.

Ultraviolet spectrum: λ_{max} 223 mμ (ε 5800).



The corresponding *methyl ester* (XLVII) was obtained by the action of diazomethane upon the acid (XIX). The latter (20 g) was dissolved in 200 cm³ of warm anhydrous dioxane. The solution was cooled to 5° and treated with 1 mole of diazomethane in ether. The solvents were immediately concentrated, first at atmospheric, and later at reduced pressure, to about 50 cm³. After most of the ether had been removed, the temperature was kept below 30°. When ether was added to the concentrated dioxane solution, crystallization set in immediately. After the mixture had been kept at 0° for 3 hr, 19 g of the ester (XLVII), m.p. 130–131°, were collected. Another gram of the ester was recovered from the mother liquors. Total yield: 20 g (95 per cent). For analysis the ester was recrystallized twice from acetone/petroleum ether and dried 6 hr at 60° in high vacuum, m.p. 132°.

Anal. Calcd. for $C_{12}H_{14}O_5$: C, 60·50; H, 5·92. Found: C, 60·46; H, 6·12.



Lactonization of the hydroxy acid (XIX): *The oxido lactone* (XXVIII). A mixture of the oxido acid (XIX) (15·4 g), sodium acetate (3·1 g), acetic anhydride (15·5 cm³)

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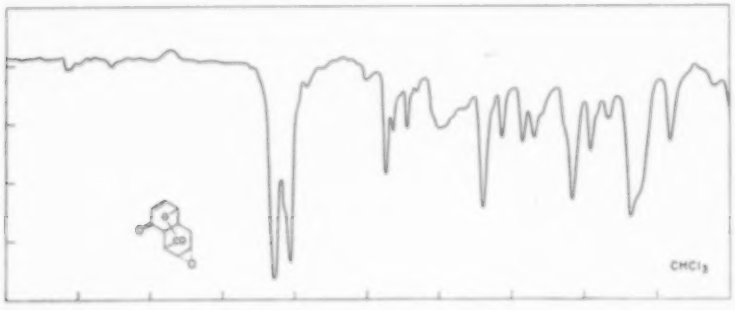
and benzene (300 cm³) was heated under reflux for 4 hr. The reaction mixture was then cooled, ethyl acetate (300 cm³) and some chipped ice were added, and the resulting mixture was washed with cold 5 per cent sodium bicarbonate solution. The two phases were filtered together to remove a small amount of polymeric material which hindered separation, and the bicarbonate layer was washed twice with ethyl acetate and once with chloroform. The combined organic phases were dried over sodium sulfate and evaporated to yield an oil which slowly solidified. This product was triturated with ethyl acetate and filtered to yield 5·8 g (41 per cent) of the lactone (XXVIII), m.p. 172–177°. For analysis the lactone was crystallized from acetone to give colorless prisms, m.p. 177–177·5°.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64·07; H, 4·89. Found: C, 64·13; H, 4·95.

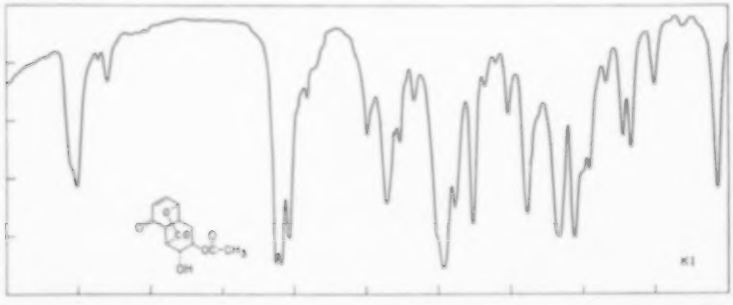
Ultraviolet spectrum: λ_{max} 219 mμ (ε 6160).



Cleavage of the oxide (XXVIII): *The hydroxy acetate* (XXIX). The oxide (XXVIII) (5·2 g), trifluoroacetic acid (5·2 cm³), and glacial acetic acid (390 cm³) were heated under reflux for 2 hr. The solvent was then evaporated *in vacuo* to give a solid residue which, when washed with acetone, gave 1·93 g of colorless crystalline material, m.p. 224–226°. The acetone wash liquor was concentrated and treated with ether to give a second crop, 2·66 g, which was crystallized from acetone/benzene to yield 1·85 g of product, m.p. 229–231°. The analytical sample of the hydroxy acetate (XXIX), obtained by recrystallization from acetone/benzene, had m.p. 232–233°.

Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58·64; H, 5·30. Found: C, 58·87; H, 5·48.

Ultraviolet spectrum: λ_{max} 223 mμ (ε 6600).



When the oxido acid (XIX) was treated with acetic acid containing trifluoroacetic acid under conditions identical with those just described, no pure product could be isolated, but the ultraviolet and infrared spectra of the crude materials obtained

indicated clearly that aromatization had occurred to a considerable extent (cf. footnote p. 9).

Methylation of the hydroxy acetate (XXIX): *The methoxy acetate* (XXXI). The hydroxy acetate (XXIX) (1·29 g), dissolved in 52 cm³ of dioxane, was treated with 39 cm³ of methyl iodide, 20 g of freshly prepared silver oxide and 20 g of anhydrous sodium sulfate. This mixture was heated under reflux, with stirring, for 1 hr, and then filtered through a sintered glass plate. After the filtrate had been taken to dryness *in vacuo*, the residue was dissolved in ethyl acetate and filtered through 15 g of neutral aluminium oxide (activity II/III). When the eluate was concentrated to a small volume and treated with some drops of ether, 557 mg (41 per cent) of methoxy acetate (XXXI), m.p. 162–165°, separated. For analysis the compound was crystallized from ethyl acetate/ether, to give heavy glassy prisms, m.p. 167–169°, which were dried at 70° in high vacuum for several hours.

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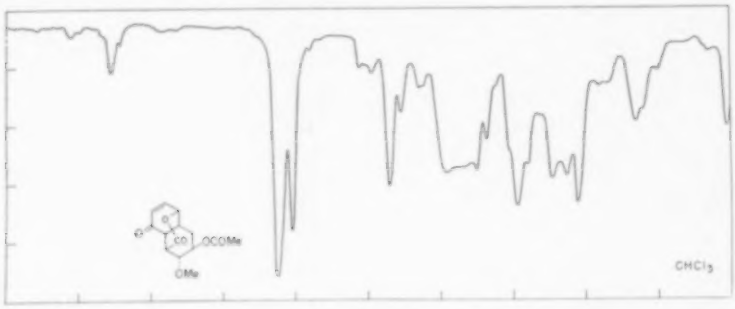
Anal. Calcd. for $C_{14}H_{16}O_6$: C, 59·99; H, 5·75; OMe, 11·07. Found: C, 60·08; H, 6·02; OMe, 11·03.

Ultraviolet spectrum: λ_{max} 222 mμ (ε 5880).



From the mother liquors, after separation of the methoxy acetate (XXXI), the *C-methylated compound* (iii) was isolated by careful chromatography on aluminium oxide (activity II/III). The substance was eluted in the early fractions of the chromatogram, using benzene containing 20 per cent of ethyl acetate. The material in these fractions had m.p. 144–145°. Further crystallization from acetone gave colorless needles, m.p. 152–153°. This substance forms a continuous series of mixed crystals with the methoxy acetate (XXXI). The melting point of a mixture of (XXXI) and (iii) was 136–155°. For analysis, (iii) was dried overnight in high vacuum at 80°.

Anal. Calcd. for $C_{15}H_{18}O_6$: C, 61·21; H, 6·17; OMe, 10·55. Found: C, 61·28; H, 6·35; OMe, 10·88.

Ultraviolet spectrum: λ_{max} 234 mμ (ε 7700).

Hydrogen peroxide oxidation of the methoxy acetate (XXXI): *The oxide* (XXXII). The methoxy acetate (XXXI) (180 mg) in pyridine (7 cm³) and hydrogen peroxide (1·4 cm³ of 30 per cent solution) was allowed to stand at room temperature for 18 hr. The reaction mixture was then poured onto ice. The product was extracted with ethyl acetate, and the organic layer washed with dilute hydrochloric acid, saturated sodium bicarbonate solution, and saturated sodium chloride solution. The extract was dried and evaporated, and the colorless oily residue was crystallized from ether to give 62 mg of the oxide (XXXII), m.p. 165–168°. The analytical sample, obtained by recrystallization from acetone/ether, formed plates, m.p. 169–170°.

Anal. Calcd. for $C_{14}H_{16}O_7$: C, 56·75; H, 5·44. Found: C, 56·77; H, 5·58.

Ultraviolet spectrum: no absorption of high intensity above 210 mμ.

Oxidation of the methoxy acetate (XXXI) *by osmium tetroxide.* Osmium tetroxide (82 mg), dissolved in dry benzene (1·25 cm³), was added to a solution of the methoxy acetate (XXXI) (70 mg) in absolute benzene (2 cm³) containing pyridine (0·05 cm³). The mixture was allowed to stand at room temperature for 15 hr. During this time 138 mg (80 per cent) of the osmium complex (XXXIII), m.p. 175–182° (*dec.*), separated as brown prisms. For analysis the material was crystallized from dichloromethane, m.p. 180–190° (*dec.*).

Anal. Calcd. for $C_{24}H_{28}O_{10}N_2Os$: N, 4·04. Found: N, 4·21.

Zinc reduction of the methoxy acetate (XXXI): *The unsaturated acid* (ix). The methoxy acetate (XXXI) (200 mg) was dissolved in acetic acid (2 cm³) and water (0·65 cm³). To the cooled, well-stirred, solution, 400 mg of zinc powder were added all at once; the cooling was such as to keep the temperature below 15°. Stirring was continued for 8 min, and the reaction mixture was then poured into 100 cm³ of ethyl acetate. The solution was then shaken with water and saturated sodium chloride solution, dried over sodium sulfate, and taken to dryness *in vacuo* at 30–50°. The crystalline residue (200 mg) was washed with cold acetone. The fine prisms of (ix) so obtained melted at 165–168°, resolidified in needles, and melted again at 207–215°. For analysis the material was dried in high vacuum at 80° for several hours.

Anal. Calcd. for $C_{14}H_{18}O_6$: C, 59·56; H, 6·43. Found: C, 59·84; H, 6·64.

The infrared spectrum ($CHCl_3$) possessed bands at 5·73 and 5·80 μ.

The above acid (ix) was transformed into its *methyl ester*, and thence into the corresponding *ethylene thioketal.* The acid (ix) (200 mg) was dissolved in 5 cm³ of methanol, diluted with 5 cm³ of ether, and treated with an excess of ethereal diazomethane solution at 0°. After 5 min the solution was taken to dryness *in vacuo* and the residue was dissolved in 2 cm³ of acetic acid. Ethylene dithiol (0·3 cm³) and boron trifluoride etherate (0·2 cm³) were added, and the reaction mixture was allowed to stand at room temperature for 1 hr. The solvent was then removed *in vacuo*, the yellowish residue was dissolved in dichloromethane/ether (1 : 1) and shaken with water, sodium bicarbonate solution, and saturated sodium chloride solution. The organic phase was dried with sodium sulfate, and evaporated to dryness. When the yellow residue was distilled in high vacuum, 166 mg of colorless distillate was obtained which was chromatographed on 10 g of neutral alumina (activity II/III). Dichloromethane/benzene (1 : 1) eluted 133 mg of crystalline material. For analysis the *ethylene thioketal* was crystallized twice from ether/petroleum ether, to give colorless prisms, m.p. 112–113°, which were dried in high vacuum for several hours at 80°.

Anal. Calcd. for $C_{17}H_{24}O_5S_2$: C, 54·83; H, 6·50; S, 17·15. Found: C, 55·01; H, 6·55; S, 17·40.

The five-membered lactone series

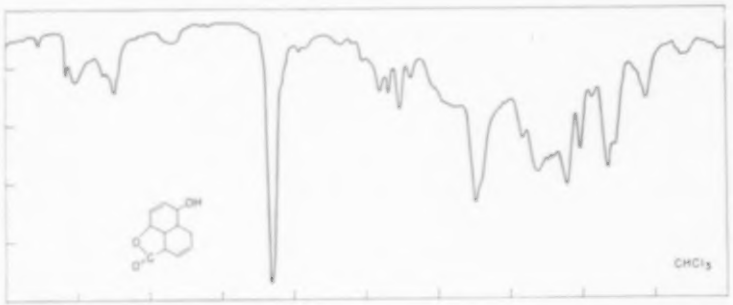
Preparation of the five-membered lactone (XXXIV). This substance is preparable by aluminium *iso*propoxide reduction of the ester adduct (IV : R = Me), the lactone (XIII), or the hydroxy ester (XXXVII).

Method (a). *From the lactone* (XIII) *or the hydroxy ester* (XXXVII). The lactone (XIII) (5 g), or the ester (XXXVII) (5 g), and freshly distilled aluminium *iso*propoxide (6 g) were added to 80 cm³ of anhydrous *iso*propanol, in a flask equipped with a stirrer,

a Vigreux column, and separatory funnel. The reaction mixture was stirred, and heated at such a rate that slow distillation took place; *iso*propanol was introduced at such a rate as to keep the reaction mixture approximately at constant volume. After the distillation of acetone had ceased (about 45 min), the reaction mixture was kept under gentle reflux for another 45 min. The solvent was then removed *in vacuo*. The foamy residue was dissolved in ethyl acetate (80 cm^3), and the resulting milky solution was cooled to 0° and added to a solution of sodium potassium tartrate (83 g) and sodium bicarbonate (6·3 g) in water (125 cm^3). The mixture was shaken and the two phases were separated. The aqueous phase was extracted three times further with ethyl acetate. The combined ethyl acetate extracts were washed once with ice-cold sodium bicarbonate, once with saturated sodium chloride solution, and dried over sodium sulfate. When the solvent was removed, 4·5 g of a colorless crystalline solid remained. Recrystallization from acetone/ether gave 3·7 g of the hydroxy lactone (XXXIV), m.p. 120–122°. For analysis the lactone was recrystallized once from acetone/ether; prisms, m.p. 122–123°.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68·73; H, 6·29. Found: C, 68·79; H, 6·50.

Ultraviolet spectrum: end absorption.



Method (b). *From the ester adduct* (IV : R = Me). The ester adduct (440 mg) and aluminium *iso*propoxide (1·83 g) were dissolved in dry *iso*propanol (8 cm^3). The mixture was boiled gently, and acetone and *iso*propanol were distilled slowly from the reaction mixture through a short column. From time to time *iso*propanol was added to maintain a constant volume. After one hour no more acetone could be detected in the distillate. The reaction mixture was then concentrated under reduced pressure, treated with ice-cold 2 N hydrochloric acid, and extracted with methylene chloride/ether (1 : 3). The organic phase was washed with sodium bicarbonate and saturated sodium chloride solution, and taken to dryness *in vacuo*. The residue was crystallized twice from acetone/ether, to give 230 mg of colorless prisms of the lactone (XXXIV), m.p. 119–120°, identical with the material prepared by method (a).

Oxidation of the lactone (XXXIV): *The ketone* (XXXVIII). To a solution of the hydroxy lactone (XXXIV) (1 g) in acetone (50 cm^3), 1·90 cm^3 of chromic acid oxidation mixture (92 cm^3 concentrated sulfuric acid, 290 cm^3 of water, 106 g chromium trioxide) were added slowly with stirring at room temperature. A slight excess of chromic acid was then destroyed by adding two drops of butanol. The reaction mixture was filtered quickly through a small column of aluminium oxide (activity II/III), and the filtrate was taken to dryness. Crystallization from acetone/ether gave 830 mg of the *ketone* (XXXVIII) as colorless prisms, m.p. 125–126°. For analysis the material

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was crystallized once again from acetone/ether and dried for several hours at 80° in high vacuum, m.p. 126–128°.

Anal. Calcd. for $C_{11}H_{10}O_2$: C, 69·46; H, 5·30. Found: C, 69·50; H, 5·43.

Ultraviolet spectrum: λ_{max} 216 mμ (ε 8500).

Infrared spectrum ($CHCl_3$): 5·65 and 5·95 μ.

Oxidation of the keto lactone (XXXVIII) *by perbenzoic acid.* To a solution of the keto lactone (XXXVIII) (600 mg, 3·16 mmoles) in dioxane (2 cm³), 7 cm³ of a benzene solution of perbenzoic acid (0·575 M) was added. Dioxane was then added to bring the total volume to 10 cm³. The reaction mixture was allowed to stand at room temperature for 10 hr, during which time a solid separated. When the colorless crystalline material (206 mg, m.p. 185–187·5°) was collected, and recrystallized from ethyl acetate, the *dilactone* (XLI) was obtained as colorless prisms, m.p. 189–193° (*dec.*).

Anal. Calcd. for $C_{11}H_{10}O_5$: C, 59·46; H, 4·54. Found: C, 59·26; H, 4·68.

Ultraviolet spectrum: end absorption ($\varepsilon_{210\ m\mu}$ 5500).

Infrared spectrum (KI): 5·67 μ, 5·70 μ, 6·04 μ (weak).

Action of iodine/silver acetate on the keto lactone (XXXVIII). To a well-stirred suspension of the keto lactone (XXXVIII) (498 mg) and silver acetate (522 mg) in glacial acetic acid (13 cm³), finely powdered iodine (684 mg) was added all at once. The reaction mixture was stirred for 2 hr 30 min. Silver iodide was removed by filtration through Celite, which was washed three times with hot chloroform. The filtrate was evaporated to dryness *in vacuo* at 40°. The brown residual oil was taken up in chloroform/ethyl acetate (1 : 3) and washed with 0·1 N sodium thiosulfate, saturated sodium bicarbonate solution, and water. When the dried organic layer was evaporated at the water pump, a colorless oil was obtained, which crystallized from acetone/dichloromethane to yield 330 mg of colorless prisms of the *iodo acetate*, m.p. 156–158° (*dec.*). The analytical sample, obtained by recrystallization from a large volume of dichloromethane had m.p. 161–162° (*dec.*).

Anal. Calcd. for $C_{13}H_{13}O_5I$: C, 41·40; H, 3·49; I, 33·70. Found: C, 41·72; H, 3·49; I, 34·07.

Ultraviolet spectrum: end absorption ($\varepsilon_{210\ m\mu}$ 10,000).

Infrared spectrum: 5·64 μ, 5·80 μ, 5·95 μ.

Zinc reduction of the keto lactone (XXXVIII). The keto lactone (XXXVIII) (600 mg) was dissolved in acetic acid (6 cm³) and water (2·6 cm³). While the mixture was stirred vigorously, and kept at 15°, zinc powder (1·2 g) was added all at once. After 10 min the reaction mixture was diluted with ethyl acetate, filtered, and the filtrate was washed with dilute hydrochloric acid and saturated aqueous sodium chloride solution. The organic phase was dried with anhydrous sodium sulfate, and taken to dryness *in vacuo*. The residue was taken up in acetone, treated with a small amount of Norite and filtered. When the filtrate was concentrated to a small volume and treated with a few drops of ether, 420 mg of the acid (XXXIX), m.p. 123–127°, separated. For analysis the acid was recrystallized twice from acetone/ether, from which it separated as colorless needles, m.p. 124–127°.

Anal. Calcd. for $C_{11}H_{12}O_5$: C, 68·73; H, 6·29. Found: C, 68·51; H, 6·49.

Infrared spectrum ($CHCl_3$): 5·83 and 5·85 μ.

The above *β,γ-unsaturated keto acid* was isomerized to the conjugated isomer (XL) by potassium acetate in ethanol. The acid (XXXIX) (100 mg), potassium acetate

(100 mg), and absolute ethanol (5 cm³) were heated under reflux in an atmosphere of nitrogen for 3 hr. The solvent was then evaporated *in vacuo* and the residue was taken up in ethyl acetate and water. The organic layer was washed three times with saturated sodium chloride solution, dried, and evaporated *in vacuo*. When the colorless residual oil was crystallized from ether, 60 mg of the acid (XL), m.p. 163–165°, were obtained. The analytical sample, obtained by recrystallization from dichloromethane/ether formed colorless prisms, m.p. 165–166°.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 68·73; H, 6·29. Found: C, 68·63; H, 6·51.

Ultraviolet spectrum: λ_{max} 223 mμ (ε 7400).

Infrared spectrum ($CHCl_3$): 5·85 μ and 5·97 μ.

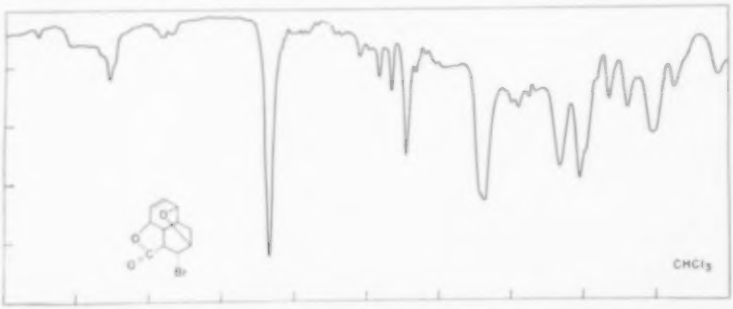
The above acid (XL) was converted to the corresponding *methyl ester* by treatment with excess ethereal diazomethane. Crystallized from acetone/ether, the ester had m.p. 77–78°.

Infrared spectrum ($CHCl_3$): 5·79 and 6·0 μ.

Bromination of the hydroxy lactone (XXXIV): *The bromo lactone* (LVIII). *Method* (a). *In methanol*: The hydroxy lactone (XXXIV) (23 g) in methanol (230 cm³) was treated with a solution of bromine (19·2 g) in methanol (200 cm³). After the mixture had stood at room temperature for 45 min, sufficient solid sodium bicarbonate was added to neutralize the hydrobromic acid, and the solution was then concentrated to approximately 30 cm³. A large volume of methylene chloride was added, and the mixture was washed twice with water, once with sodium bicarbonate solution, once with saturated sodium chloride solution, and the organic phase was dried over anhydrous sodium sulfate. The solvent was then removed *in vacuo*, and the residual yellow oil was taken up in acetone and ether, and allowed to stand in the cold for 24 hr. Fifteen grams of the bromo lactone (LVIII), m.p. 120–124°, separated. For analysis the substance was recrystallized four times from acetone/ether, m.p. 129–130°.

Anal. Calcd. for $C_{11}H_{11}O_3Br$: C, 48·72; H, 4·09; Br, 29·47. Found: C, 48·53; H, 4·21; Br, 29·30.

Ultraviolet spectrum: end absorption.



Method (b). *In methylene chloride*. The hydroxy lactone (XXXIV) (20 g) was dissolved in methylene chloride (500 cm³). Bromine (5·4 cm³) was added slowly at room temperature, and the reaction mixture was allowed to stand for 20 min. It was then cooled in an ice-bath and extracted once with aqueous sodium bicarbonate, containing a small amount of sodium thiosulfate, and once with sodium bicarbonate alone. The organic phase was then washed with saturated sodium chloride solution

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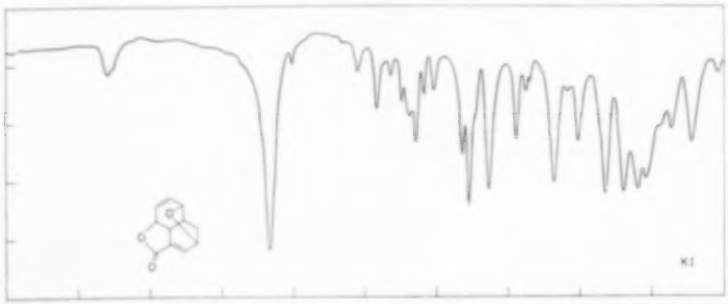
and dried over anhydrous sodium sulfate. The solvent was removed, and the residual yellow oil was taken up in acetone and ether. When the solution was allowed to stand, 21 g of the bromo lactone (LVIII), m.p. 122–125°, separated. This material was sufficiently pure to be converted directly into the methoxy ether (LIII) (see below), in approximately 80 per cent yield. However, it was contaminated with a small amount of a relatively insoluble high-melting substance, which frequently separated first from the acetone/ether solution of the crude product. The high-melting material is a *dibromide*; for analysis it was recrystallized three times from acetone, and had m.p. 175–176°.

Anal. Calcd. for $C_{11}H_{12}O_3Br_2$: C, 37·53; H, 3·44; Br, 45·40. Found: C, 38·00; H, 3·34; Br, 45·41.

Preparation of the unsaturated ether (XLVI). To a three-necked flask fitted with an efficient stirrer and a short Vigreux column, 10 g of the oxido lactone (XXVIII), 29·6 g of aluminium *iso*propoxide and 166 cm³ of anhydrous *iso*propanol were added. The reaction mixture was heated at such a rate that acetone distilled as it was formed. After 3 hr the distillate gave a negative reaction with 2,4-dinitrophenylhydrazine reagent. The reaction mixture was then concentrated to dryness *in vacuo* and the residue was dissolved in 150 cm³ of ethyl acetate. The mixture was stirred with 300 cm³ of a saturated Rochelle's salt solution (containing 66 g of sodium potassium tartrate and 5 g of sodium bicarbonate per 100 cm³ of water). The aqueous solution was extracted three times with ethyl acetate and the combined organic layers were dried over sodium sulfate. When the solvent was removed, an oily residue was obtained, which could be used directly for the preparation of the methoxy lactone (LIII) (see below). In the present experiment, the oil was dissolved in methylene chloride and filtered through deactivated aluminium oxide. The methylene chloride was removed *in vacuo* and the residue was crystallized from ethyl acetate/ether. The unsaturated lactone (XLVI) was obtained in 43 per cent yield as colorless prisms, m.p. 124–126°.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69·46; H, 5·30. Found: C, 69·34; H, 5·41.

Ultraviolet spectrum: λ_{max} 228 mμ (ε 3140).

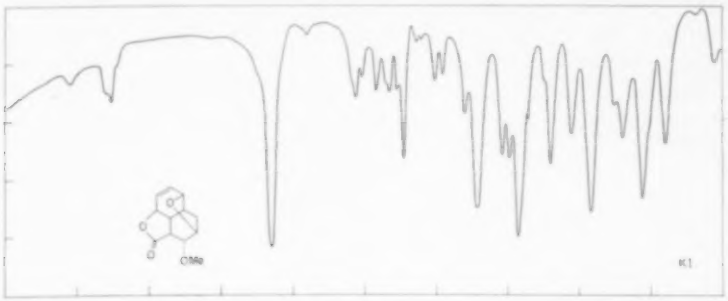


Preparation of the methoxy ether (LIII). *Method* (a) The crude oily unsaturated ether (XLVI), whose preparation is described immediately above, was taken up in 260 cm³ of anhydrous methanol containing 280 mg of sodium methoxide, and allowed to stand at room temperature for 90 min. The reaction mixture was then made acidic with glacial acetic acid and all solvents were removed *in vacuo*. The residue was taken up in methylene chloride, which was washed with water and dried over anhydrous sodium sulfate. The methylene chloride solution was concentrated to

about 60 cm³ and filtered through a short column of aluminium oxide (activity II/III). The column was washed with methylene chloride, and the eluate (about 200 cm³) was evaporated to give an oil which solidified slowly. Crystallization from a mixture of ethyl acetate (5 cm³) and ether (5 cm³) gave 5 g of the *methoxy ether* (LIII) as colorless needles, m.p. 95–98°. For analysis the material was recrystallized from ethyl acetate/ether, m.p. 103–104°.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64·85; H, 6·35; OMe, 13·96. Found: C, 65·11; H, 6·46; OMe, 13·86.

Ultraviolet spectrum: no absorption.



Method (b). Twenty-three grams of oxido ester (XLVII) and freshly distilled aluminium *iso*propoxide (30 g) were dissolved in anhydrous *iso*propanol (400 cm³). The mixture was stirred, and heated at such a rate that slow distillation through a short Vigreux column took place. During the distillation, *iso*propanol was replaced at such a rate as to maintain the reaction mixture at constant volume. After about 5 hr no acetone could be detected in the distillate (2,4-dinitrophenylhydrazine reagent). After the reduction was complete, the mixture was kept under gentle reflux for a further 2 hr. The solvent was then completely removed *in vacuo*, and the foamy residue was taken up in 375 cm³ of ethyl acetate. The resulting solution was cooled to 0° and added to a solution of sodium potassium tartrate (410 g) and sodium bicarbonate (31 g) in water (625 cm³). The mixture was shaken well, and the two phases were separated. The aqueous phase was extracted three times with ethyl acetate. The combined ethyl acetate phases were washed twice with ice-cold sodium bicarbonate, once with saturated sodium chloride solution and dried over anhydrous sodium sulfate. When the solvent was removed *in vacuo*, 21 g of a partially crystalline brown product were obtained. This material was dissolved in the smallest possible amount of dichloromethane and allowed to stand at room temperature for 2 hr; occasionally a considerable amount of crystalline material did not dissolve in the methylene chloride at all. The dichloromethane-insoluble material, and that which separated from the methylene chloride solution on standing, were collected and washed with methylene dichloride. Three grams of this by-product, m.p. 175–176°, which is probably the *dihydroxy ester* (xii), were obtained. For analysis the substance was recrystallized three times from acetone and dried for 12 hr at 80° in high vacuum, m.p. 175–176°.

Anal. Calcd. for $C_{14}H_{20}O_5$: C, 62·67; H, 7·51. Found: C, 62·88; H, 7·65.

Ultraviolet spectrum: no absorption.

Infrared spectrum ($CHCl_3$): single sharp band at 5·81 μ.

The combined filtrates from the above by-product were concentrated and dried

in high vacuum. The residue was dissolved in 400 cm³ of anhydrous methanol. One hundred and twenty cm³ of a sodium methoxide solution (made up by dissolving 1 g of sodium in 500 cm³ of anhydrous methanol) were added, and the mixture, which turned brown, was kept at room temperature for 90 min. The solution was then neutralized with glacial acetic acid and the solvents were removed *in vacuo*. The residue was dissolved in methylene chloride, and the solution was washed twice with small amounts of water and then with saturated sodium chloride solution. The dried (anhydrous sodium sulfate) solution was concentrated to small volume and filtered through a short column of neutral aluminium oxide (activity II/III). The eluate was concentrated to a very small volume, and ether was added. Crystallization of the desired *methoxy ether* (LIII) began at once. After the mixture had been kept at 0° for 2 hr, 7·6 g of the methoxy ether (LIII), m.p. 100–102°, were collected. This material was identical with that prepared by method (a) above. After the mother liquors had been treated once again with methoxide, as above, a further 700 mg of the methoxy ether were obtained.

Method (c). The bromo lactone (LVIII), m.p. 122–125°, (see above), (16·5 g) was dissolved in anhydrous methanol (260 cm³). Ninety-five cm³ of a sodium methoxide solution (made up by dissolving 2 g of sodium in 100 cm³ of anhydrous methanol) were added, and the yellow mixture was kept at room temperature for 2 hr 30 min. The reaction mixture was then neutralized with glacial acetic acid, and concentrated *in vacuo* to approximately 10 cm³. Methylene chloride and some ice-cold water were added, and the mixture was shaken. The two phases were separated, and the organic phase was washed once with ice-cold sodium bicarbonate solution, once with saturated sodium chloride solution, and dried over anhydrous sodium sulfate. Removal of the solvents gave a crystalline residue from which 11·3 g of the *methoxy ether* (LIII) were obtained by recrystallization from acetone/ether. The material melted at 100–102°, and was identical with that obtained by methods (a) and (b) above.

Degradation of the methoxy ether (LIII). A, *to the methoxy lactone* (LVI). The methoxy ether (LIII) (60 mg) was dissolved in acetyl chloride (2 cm³). Stannic chloride (0·2 cm³) was added, and the reaction mixture was allowed to stand at room temperature for 15 min. The solvents were then removed *in vacuo*, the residue was taken up in ethyl acetate, and washed with water, sodium bicarbonate solution, and water again. The ethyl acetate solution was dried over sodium sulfate and concentrated to dryness *in vacuo*. The residual oil was distilled, and the first fraction, a colorless oil (b.p. $_{0\cdot08\ mm}$ 110–125°), crystallized. When the material was recrystallized from methylene chloride/ether, 32 mg of the *lactone* (LVI), m.p. 119–122°, were obtained. For analysis the material was crystallized thrice from dichloromethane/ether, m.p. 123–124°.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70·57; H, 5·92; OMe, 15·19. Found: C, 70·95; H, 6·17; OMe, 15·26.

Ultraviolet spectrum: $\lambda\lambda_{max}$ ~253 mμ, ~260 mμ, 266 mμ, 273 mμ ($\varepsilon\varepsilon$ 258, 345, 468, 495).

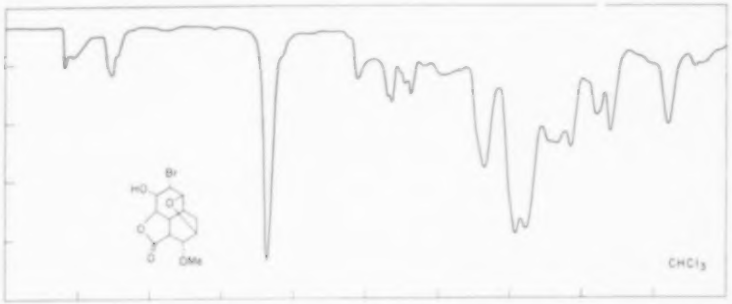
Infrared spectrum ($CHCl_3$): 5·60 μ.

B, *to α-naphthoic acid*. The methoxy ether (LIII) (80 mg) and freshly sublimed pyridine hydrochloride (400 mg) were sealed together in a highly evacuated Pyrex glass tube, and heated for 5 min at 190–200°. The cooled reaction mixture was

dissolved in 2 N hydrochloric acid and extracted with methylene chloride. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness, leaving 55 mg of colorless crystalline residue. After one recrystallization from methylene chloride, it melted at 152–156°. The material was then partitioned between sodium bicarbonate and ether in the usual way. When the acidic fraction was crystallized from benzene, colorless needles of α-naphthoic acid, m.p. 160–162°, identical with an authentic sample, were obtained, m.m.p. 160–162°. The infrared spectrum of the degradation product and that of an authentic specimen of α-naphthoic acid were identical.

Preparation of the bromohydrin (LIX), *and of the ketone* LXIII). The methoxy ether (LIII) (7 g) was dissolved in water (63 cm³) and 1 N sulfuric acid (12·6 cm³), with stirring, and heating to 80°. To the stirred solution, which was kept between 60–70°, N-bromosuccinimide (5·85 g) was added over a period of 10 min. The reaction mixture was then maintained at 80–90° for 30 min. At the end of that time the potassium iodide-starch test was practically negative. A small quantity of sodium bisulfite was then added to destroy excess N-bromosuccinimide, and the aqueous solution was extracted continuously with methylene dichloride for 4 hr. When the solvent was evaporated, 12·92 g of the crude bromohydrin (LIX) were obtained as a yellow oil. Ordinarily, this crude material was oxidized directly to the corresponding ketone. However, if it was taken up in acetone, crystalline bromohydrin separated. After several further crystallizations from acetone, in order to effect separation from succinimide, the bromohydrin (LIX) was obtained as a colorless solid, m.p. 150–151°.

Anal. Calcd. for $C_{12}H_{15}O_5Br$: C, 45·13; H, 4·74; Br, 25·04. Found: C, 45·24; H, 4·86; Br, 25·13.



The above crude oily bromohydrin (LIX) (12·92 g) was dissolved in 53 cm³. of hot glacial acetic acid. The solution was cooled to room temperature and chromic acid (5·3 g) dissolved in water (2·7 cm³) and acetic acid (27 cm³) was added. The solution became warm, and after 2 min the bromo ketone began to crystallize. The reaction mixture was allowed to stand at room temperature for ten hours. The ketone which had separated (6 g, 60 per cent) was collected and washed with acetic acid and ether. For recrystallization, the crude bromo ketone was extracted with acetone in a Soxhlet apparatus. The pure material crystallized directly from the extractant, and had m.p. 165–167°. For analysis the substance was recrystallized twice from ethyl acetate, m.p. 166–167°.

Anal. Calcd. for $C_{12}H_{13}O_5Br$: C, 45·44; H, 4·13; Br, 25·20. Found C, 45·45; H, 4·32; Br, 25·35.

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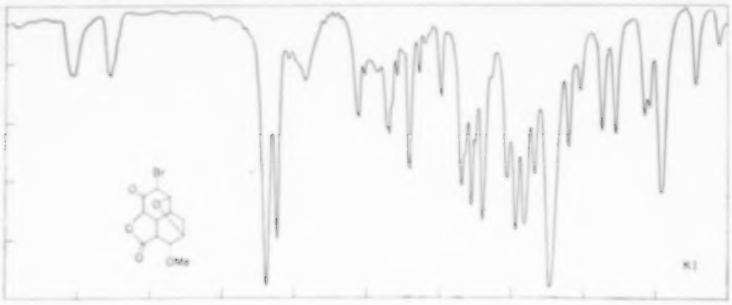


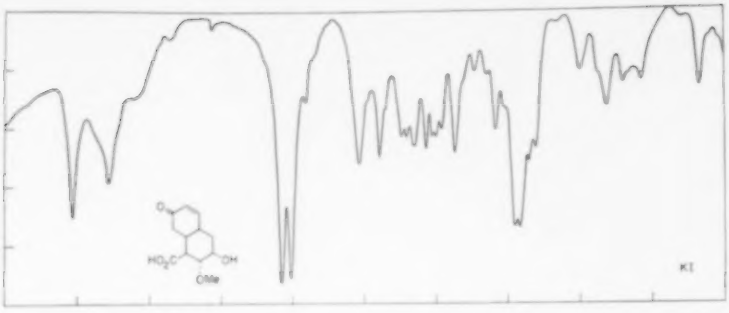
The chloro ketone (LXIII: Br = Cl). The methoxy ether (LIII) (222 mg) dissolved in water (3 cm³) was stirred at 55–60° over a period of 75 min, while 1·9 cm³ of a 2·92 per cent solution of hypochlorous acid was added slowly. The aqueous solution was then extracted continuously for 3 hr with methylene chloride. The extract was dried over sodium sulfate, and evaporated, to give 217 mg of a colorless oil which solidified in part. This material was dissolved in acetone (20 cm³), and 0·38 cm³ of chromic acid solution (prepared by dissolving 92 g of concentrated sulfuric acid and 106 g of chromic acid in 290 cm³ of water) were added slowly at room temperature over a period of 1 hr. The excess chromic acid was then destroyed by addition of *iso*propanol, the solvents were removed *in vacuo*, and the residue was taken up in 100 cm³ of methylene chloride/ether (1 : 3). The solution was washed twice with saturated brine, and once with 5 per cent aqueous sodium bicarbonate. When the solvent was removed *in vacuo*, 178 mg of a foam were obtained from which on trituration with ethyl acetate, 63 mg of colorless crystalline material separated. After one recrystallization from ethyl acetate, 54 mg of chloro ketone were obtained as colorless prisms, m.p. 173–176°(*dec.*).

Infrared spectrum: very similar to that of the corresponding bromo ketone.

Zinc reduction of the bromo ketone (LXIII): *The acid* (LXV). The bromo ketone (LXIII) (1·87 g) was dissolved in hot glacial acetic acid (500 cm³). The solution was cooled to 17°, zinc dust (7·5 g), previously cooled to 0°, was added all at once, and the mixture was stirred vigorously for 90 sec. The zinc was then immediately removed by rapid filtration through a bed of Celite (previously prepared by suspension in acetic acid, followed by filtration), which was rinsed once with acetone. The filtrate was concentrated to dryness *in vacuo*, the residue was dissolved in 25 cm³ of water, and made basic with solid sodium bicarbonate. The basic solution was extracted continuously with ether for three hours in order to remove neutral material (34 mg). The aqueous solution was then acidified strongly (Congo), saturated with sodium chloride, and extracted continuously with ether for fourteen hours. During this time 1·03 g of the acid (LXV) separated from the boiling ether. This material had λ_{max} 227 mμ (ε 9750). After the solid was collected by filtration, the filtrate was concentrated to dryness to give a foam which crystallized on trituration with acetone, to yield a further 92 mg of product; total yield 1·12 g (79 per cent). For analysis the acid was crystallized from acetone/ethyl acetate, m.p. 204–206°.

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 59·99; H, 6·71; OMe, 12·92. Found: C, 59·96; H, 6·93; OMe, 12·88.

Ultraviolet spectrum: λ_{max} 227 mμ (ε 10,000).



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When aqueous acetic acid was used in the above reduction, the superficial phenomena resembled those just described, but the acid isolated had λ_{max} 227 mμ, with a molecular extinction coefficient of 4000–6000. The desired product (LXV) was clearly contaminated with the corresponding dihydro compound, in which the double bond at $\Delta^{5,6}$ had been saturated. These two substances formed mixed crystals which were separable only with very great difficulty. When the reduction was carried out with acetic acid and aqueous dioxane, the *dihydroxy acid* (xvi) was produced. The bromo ketone (150 mg) was dissolved in 15 cm^3 of a dioxane solution, prepared from 94 cm^3 of dioxane, 3 cm^3 of water and 3 cm^3 of acetic acid. Zinc dust (150 mg) was added all at once, and the resulting mixture was stirred vigorously at room temperature for 6 min. The zinc was removed by filtration, the filtrate was concentrated *in vacuo* to approximately 2 cm^3, and 25 cm^3 of water were added. The solution was made basic with solid sodium bicarbonate and extracted continuously with ether for three hours to remove neutral material (25 mg). The aqueous solution was then acidified and extracted continuously with ether for fourteen hours. The crude product so obtained (109 mg) was triturated with ethyl acetate/ether, and gave 48 mg of the acid (xvi).

Anal. Calcd. for $C_{12}H_{16}O_6$: C, 56·24; H, 6·29; OMe, 12·09. Found: C, 56·22; H, 6·52; OMe, 12·10.

Ultraviolet spectrum: λ_{max} 228 mμ (ε 9000).

Infrared spectrum (KI): 5·80 and 5·96 μ.

For preparation of the corresponding *methyl ester*, the above acid (39 mg) was dissolved in dioxane and treated with excess ethereal diazomethane. The dioxane was removed *in vacuo*, and the residue was triturated with ethyl acetate/ether. Thirty-four milligrams of crystalline, very insoluble, methyl ester were obtained. For analysis the substance was recrystallized from acetone/ether, m.p. 185–186°.

Anal. Calcd. for $C_{13}H_{18}O_6$: C, 57·77; H, 6·71. Found: C, 57·97; H, 6·72.

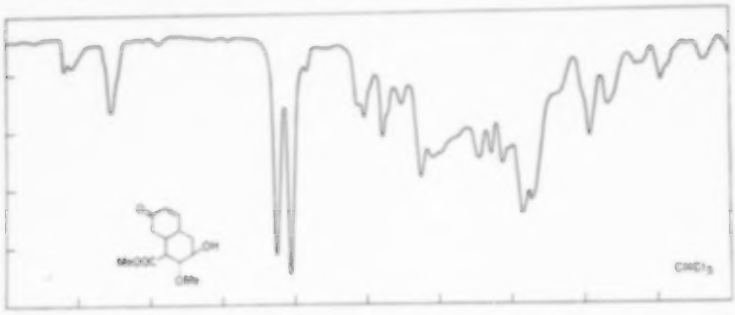
Infrared spectrum (KI): 2·94 μ, 3·04 μ, 5·77 μ, 5·98 μ.

Preparation of the acetoxy ester (LXVII). The hydroxy acid (LXV) (3·7 g) was dissolved in absolute dioxane (150 cm^3). The solution was cooled to 10° and 40 cm^3 of an ethereal diazomethane solution (1·91 per cent distilled diazomethane in absolute ether) was added slowly. The solvents were then evaporated *in vacuo* at 40°. The residual oil was dissolved in 10 cm^3 of acetone, the resulting solution was filtered, and the filtrate was evaporated to dryness *in vacuo*. When the residue was crystallized from acetone/ether, 3·76 g (96 per cent) of the *methyl ester* of the acid (LXV), m.p. 134–136°

were obtained. Four further crystallizations from acetone/ether gave an analytical sample, m.p. 139–140°.

Anal. Calcd. for $C_{13}H_{18}O_5$: C, 61·40; H, 7·14; OMe, 24·38. Found: C, 61·53; H, 7·54; OMe, 24·65.

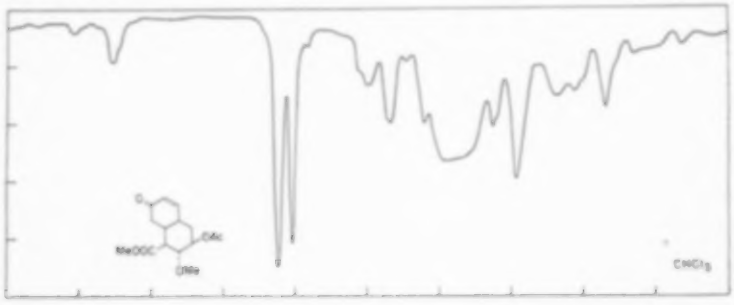
Ultraviolet spectrum: λ_{max} 225 mμ (ε 11,000).



The above *methyl ester* (3·4 g) was dissolved in absolute pyridine (18·5 cm³) and pure acetic anhydride (15 cm³). The reaction mixture was heated for two hours at 80–90° in an atmosphere of nitrogen. The solution was then cooled to room temperature and filtered. The filtrate was concentrated to dryness *in vacuo*, and the residue crystallized from acetone/ether to give 3·65 g (92 per cent) of the acetoxy ester (LXVII), m.p. 135–136°. Recrystallization from acetone/ether gave an analytical sample, m.p. 137–138°.

Anal. Calcd. for $C_{15}H_{20}O_6$: C, 60·80; H, 6·80; OMe, 20·90. Found: C, 60·58; H, 7·00; OMe, 20·43.

Ultraviolet spectrum: λ_{max} 226 mμ (ε 11,500).

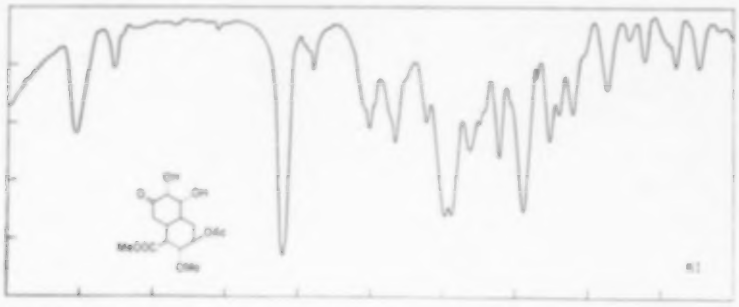


Osmium tetroxide oxidation of the unsaturated ketone (LXVII): *The diol* (LXVIII). The unsaturated ketone (LXVII) (500 mg) was dissolved, with shaking, in a solution of osmium tetroxide (463 mg) in water (50 cm³). The reaction mixture rapidly became very dark blue in color, and was allowed to stand at room temperature under nitrogen for eight hours. The solution was then placed in a separatory funnel in which 25 cm³ of carbon tetrachloride and 4·15 g of sodium chlorate had been placed. When the mixture was shaken vigorously, the blue color rapidly disappeared. The aqueous phase was extracted four times with carbon tetrachloride in order to remove the osmium oxides completely. The aqueous solution was saturated with sodium chloride and then extracted continuously with ether for 8 hr. The ethereal extract was

concentrated to a small volume, benzene was added, and the resulting solution was concentrated to dryness *in vacuo*. The residue (568 mg) was crystallized from acetone, and gave 255 mg (46 per cent) of the diol (LXVIII) as colorless needles, m.p. 169–172°. For analysis the material was recrystallized from acetone/ether, m.p. 174–175°.

Anal. Calcd. for $C_{15}H_{22}O_6$: C, 54·54; H, 6·71. Found: C, 54·72; H, 6·82.

Ultraviolet spectrum: no intense absorption above 205 mμ.



Preparation of the tetracyclic lactam (LXXII)

The lactam (LXXII). The diol (LXVIII) (800 mg) was treated with a solution of 2·3 g of periodic acid hydrate ($HIO_4 \cdot 2H_2O$) in 126 cm³ of water, and allowed to stand in an atmosphere of nitrogen for 20 min at room temperature. The colorless aqueous solution was then shaken five times with 50 cm³ portions of ethyl acetate. The organic layers were combined, washed three times with saturated brine, and dried with a large amount of anhydrous sodium sulfate. The solution was then taken to dryness under reduced pressure in an atmosphere of nitrogen at 40°. The colorless oily residue (LXIX: R = H), which occasionally solidified, was taken up in 80 cm³ of ether and treated at 0° with excess pure ethereal diazomethane. The solution was allowed to stand for 3 min at 0° and was then taken to dryness in a nitrogen atmosphere under reduced pressure at 30°. Seven hundred and ninety-six milligrams of the diester (LXIX: R = Me) were obtained as a slightly yellow oil (infrared spectrum ($CHCl_3$): 3·54 μ, 3·68 μ, 5·77 μ). The diester was taken up in 5 cm³ of benzene and treated with a supersaturated solution of 490 mg of 6-methoxytryptamine (m.p. 142°, see above) in 32 cm³ of benzene. (The hot solution of the amine was cooled quickly to 20°, and used before crystallization set in.) The reaction mixture turned cloudy immediately (separation of water) and was allowed to stand for 3 min at room temperature. It was then evaporated to dryness under reduced pressure under nitrogen at 50°. The yellow oily residual Schiff base (LXX) (infrared spectrum ($CHCl_3$): 2·90 μ, 5·76 μ, 5·99 μ, 6·13 μ) was taken up in 25 cm³ of methanol and treated with 250 mg of solid sodium borohydride. The reaction mixture was allowed to stand for 6 min at room temperature, and was then heated for 4 min on the steam bath. It was then concentrated *in vacuo* to a volume of about 5 cm³ and treated with several drops of acetic acid to destroy excess sodium borohydride. Ethyl acetate (200 cm³) was added, and the mixture was shaken four times with small volumes of 2 N hydrochloric acid. The organic layer was washed with saturated brine, dried with a large amount of anhydrous sodium sulfate, and taken to dryness *in vacuo*. In order to effect remethylation of any ester which had been hydrolyzed, the yellowish oily residue was dissolved in 10 cm³ of dioxane and treated at 10° with an excess of pure ethereal diazomethane.

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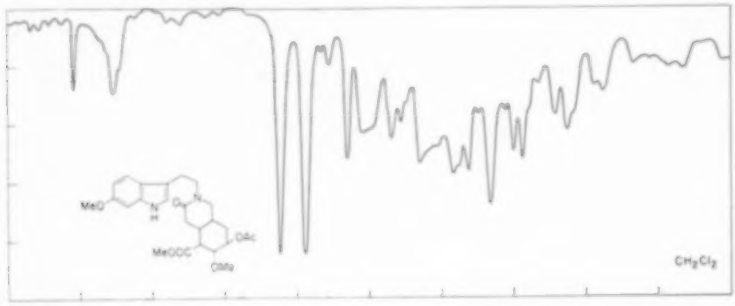
The reaction mixture was allowed to stand for 3 min at room temperature and was then taken to dryness *in vacuo*. To remove water, the residue was twice boiled for a short time with benzene and concentrated to a small volume. Finally, all of the solvent was removed in high vacuum, and the residual material (1·14 g) was treated with absolute pyridine (15 cm^3) and acetic anhydride (10 cm^3) and allowed to stand for 12 hr at 30°. The reaction mixture was then taken to dryness *in vacuo*, and the residue was dissolved in chloroform. The chloroform solution was shaken with saturated aqueous sodium bicarbonate, 2 N hydrochloric acid, and saturated brine, and then dried over anhydrous sodium sulfate. It was then concentrated to small volume, and ether was added. The *lactam* (LXXII) (923 mg) (yield 81 per cent, over-all) separated as colorless small prisms, m.p. 237–238°. For analysis the lactam was crystallized once from chloroform/ether and twice from chloroform/benzene, and dried 11 hr at 110° in high vacuum, m.p. (*vac.*) 239–240°.

Anal. Calcd. for $C_{25}H_{32}O_7N_2$: C, 63·54; H, 6·83; N, 5·93. Found: C, 63·18; H, 6·94; N, 5·91.



Model experiments on the formation and stability of Schiff bases from tryptamines. A solution in methylene chloride of 2-anisyltryptamine (0·067 mmoles/cm^3) and slightly less than one molecular equivalent of propionaldehyde gave an infrared spectrum (Fig. 1, 5·50–7·00 μ) which was constant after a few minutes, and did not

TABLE 2. 6-METHOXYTRYPTAMINE (0·067 mmole/cm^3) + EXCESS EtCHO IN CH_2Cl_2

$T_{6\cdot12\mu}$ = 20 per cent*

t (min)	$T_{5\cdot95\mu}$ (per cent)*
0	33
15	42
30	50
45	56
	†

* These intensity values are probably distorted from the true values by the presence of the intense band at 5·78 μ, arising from the excess propionaldehyde.

† In a separate experiment, at different concentrations, the 5·98 μ band was found to have disappeared virtually completely in 3 hr.

change thereafter. With a similar solution of 6-methoxytryptamine and propionaldehyde, a similar, stable, curve (Fig. 2) was observed after a few moments. By contrast, when in each case the experiment was repeated, using an excess of propionaldehyde as compared with the tryptamine, the C=N band at 5·98 μ fell with time (Tables 2 and 3).

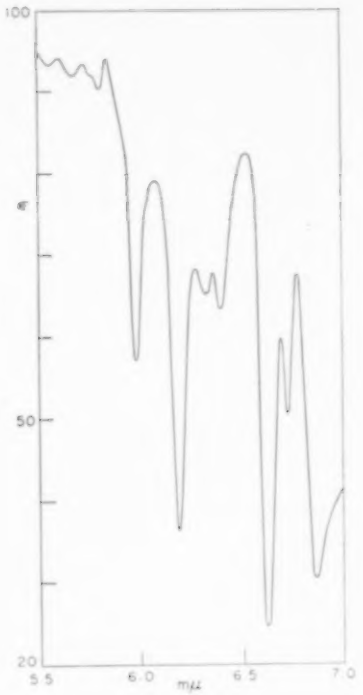


FIG. 1.

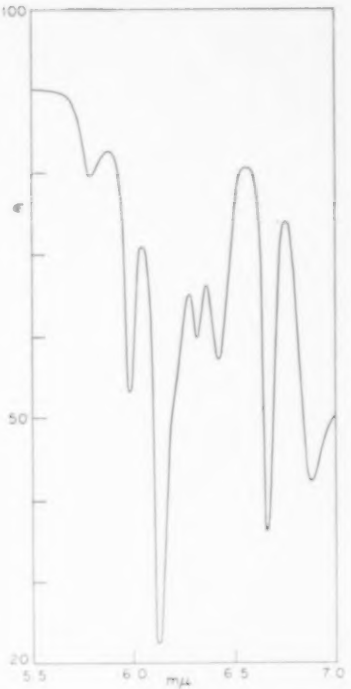


FIG. 2.

TABLE 3. 2-ANISYLTRYPTAMINE (0·067 mmole/cm³) + EXCESS EtCHO IN CH_2Cl_2

$T_{6\cdot20\mu}$ = 24 per cent*

t (min)	$T_{5\cdot88\mu}$ (per cent)*
0	32
15	39
30	42
45	44·5
60	46

* These intensity values are probably distorted from the true values by the presence of the intense band at 5·78 μ, arising from the excess propionaldehyde.

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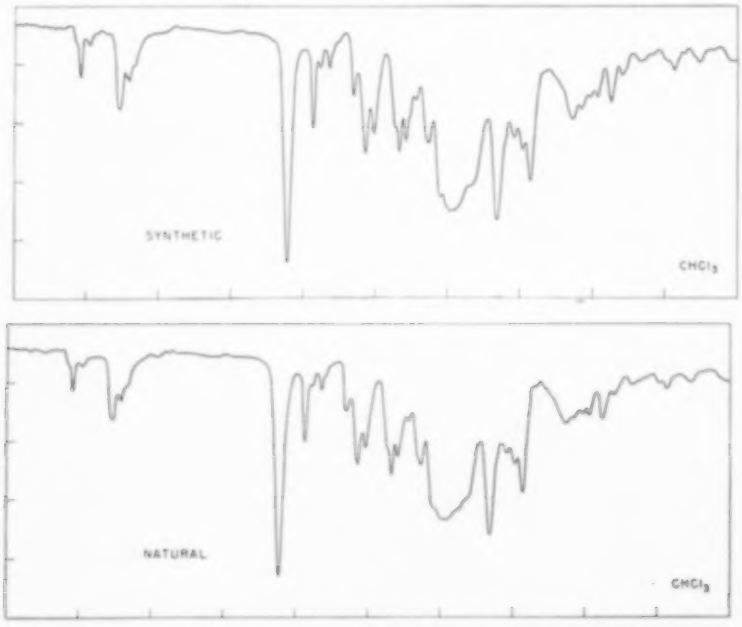
The pentacyclic series

dl Methyl-O-acetyl-isoreserpate (LXXIV). The well-dried lactam (LXXII) (m.p. 237–238°, 796 mg) was boiled gently for 2 hr in an atmosphere of nitrogen in 20 cm³ of freshly distilled phosphorus oxychloride. The solution turned green, then yellow, and finally orange. When the solvent was removed *in vacuo* in an atmosphere of nitrogen, a bright-yellow crystalline residue of the *quaternary salt* (LXXIII) was obtained. This material was thoroughly dried in high vacuum, dissolved in 20 cm³ of 90 per cent methanol, and treated in portions with 210 mg of solid sodium borohydride. The temperature of the reaction mixture was kept below 30° by occasional cooling in an ice-bath. The deep-orange color of the solution disappeared quickly, and the product began to crystallize directly from the reaction mixture in fine needles. After five minutes, 5 cm³ of water was added, the reaction mixture was cooled to 0°, the crystalline precipitate was collected and washed with water. Recrystallization from acetone/ethanol gave 536 mg of *dl* methyl-O-acetyl-*iso*reserpate (LXXIV), as colorless needles, m.p. (*vac.*) 265–266° (*dec.*). From the mother liquors 71 mg of less pure crystalline material were isolated. For analysis the ester was recrystallized twice from acetone/ethanol. The colorless needles were dried several hours at 110° in high vacuum, m.p. (*vac.*) 267–268° (*dec.*).

Anal. Calcd. for $C_{25}H_{32}O_6N_2$: C, 65·77; H, 7·07; N, 6·14. Found: C, 65·60; H, 7·11; N, 6·17.

The infrared and ultraviolet spectra of the synthetic ester were identical with those of *l* methyl-O-acetyl-*iso*reserpate derived from natural reserpine.[15]



Resolution of racemic methyl-O-acetyl-isoreserpate. The racemic ester (LXXIV) (300 mg) was dissolved in 9 cm³ of acetone and treated with a solution of di-*p*-toluyl-*l*

tartaric acid (250 mg) in acetone (3 cm³). The solution was concentrated on the steam bath to a volume of 4 cm³. It was then seeded with the di-*p*-toluyl-*l*-tartrate of *l* methyl-O-acetyl-*iso*reserpate, and allowed to crystallize. When the material which separated was recrystallized from methanol/acetone, 120 mg of colorless prisms were obtained. One further crystallization from methanol gave 98 mg of the di-*p*-toluyl-*l*-tartrate of *l* methyl-O-acetyl-*iso*reserpate, m.p. (*vac.*) 153–155° (*dec.*). The mixture melting point (*vac.*) of the synthetic salt, with an authentic specimen of the salt (m.p. (*vac.*) 151–153° (*dec.*)) was 153–155°. Ninety-five milligrams of the synthetic salt were shaken with 5 cm³ of 1 N sodium hydroxide and chloroform. The chloroform extract was washed with saturated brine, dried with sodium sulfate, and taken to dryness *in vacuo*. When the colorless residue was crystallized from acetone/ethanol, 37 mg of colorless needles of synthetic *l* methyl-O-acetyl-*iso*reserpate, m.p. (*vac.*) 287–288° (*dec.*) ($[\alpha]_D^{24}$ — 134°, *c*, 1·04 ($CHCl_3$)) were obtained. The mixture melting point (*vac.*) with *l* methyl-O-acetyl-*iso*reserpate from natural sources (m.p. (*vac.*) 284–285°, $[\alpha]_D^{24}$ — 132°, *c*, 1·04 ($CHCl_3$)) was 285–286° (*dec.*). The mother liquors from the separation of the *l,l* salt were decomposed with lye in the above manner. When the resulting free base was treated, as above, with di-*p*-toluyl-*d*-tartaric acid, it gave a salt which was recrystallized and decomposed to give *d* methyl-O-acetyl-*iso*reserpate ($[\alpha]_D^{24}$ + 130°). The infrared spectra ($CHCl_3$) of the synthetic laevorotatory and dextrorotatory bases were identical with that of the racemic base (see above).

dl Iso*reserpic acid hydrochloride*. *dl* Methyl-O-acetyl-*iso*reserpate (2·04 g) was dissolved in absolute methanol (50 cm³) and 40 per cent aqueous potash (15 cm³), and the resulting solution was heated under reflux in an atmosphere of nitrogen for 2 hr. The solution was then cooled, acidified to Congo with concentrated hydrochloric acid, and filtered to remove precipitated potassium chloride. The filtrate was taken to dryness *in vacuo*, the residue was treated with boiling methanol, and again filtered to remove potassium chloride. When the filtrate was concentrated to a small volume, and treated with an equal volume of acetone, 1·37 g of the hydrochloride, m.p. (*vac.*) 265–268° (*dec.*), separated. Concentration of the mother liquors yielded a further 0·63 g of the material, m.p. (*vac.*) 262–264° (*dec.*). For analysis the hydrochloride was recrystallized from methanol/acetone and methanol/water, m.p. (*vac.*) 267–268·5° (*dec.*).

Anal. Calcd. for $C_{22}H_{28}O_5N_2 \cdot HCl \cdot H_2O$: C, 58·07; H, 6·87; N, 6·16; Cl, 7·80. Found: C, 57·82; H, 6·78; N, 6·11; Cl, 9·31.

dl Iso*reserpic acid lactone* (LXXVIII). *dl Iso*reserpic acid hydrochloride (127 mg) and N,N′-dicyclohexylcarbodiimide (80 mg) were dissolved in dry pyridine (8 cm³). The resulting solution was heated at 100° in an atmosphere of nitrogen for 2 hr. The pyridine was then removed *in vacuo*, and the lemon-yellow residue was kept in high vacuum for 10 hr to remove the last traces of pyridine. The residue was taken up in 100 cm³ of chloroform, which was extracted four times with 1 N sulfuric acid. The combined acid solutions were washed twice with 10 cm³ portions of chloroform, and then made basic with solid sodium bicarbonate. The basic solution was extracted three times with chloroform, and the extract was dried over solid sodium sulfate. When the solvent was removed *in vacuo*, 120 mg of an oil were obtained which deposited 70 mg (67 per cent) of *dl iso*reserpic acid lactone (LXXVIII), m.p. (*vac.*) 233–234° (*dec.*), when it was triturated with ethyl acetate. For analysis the

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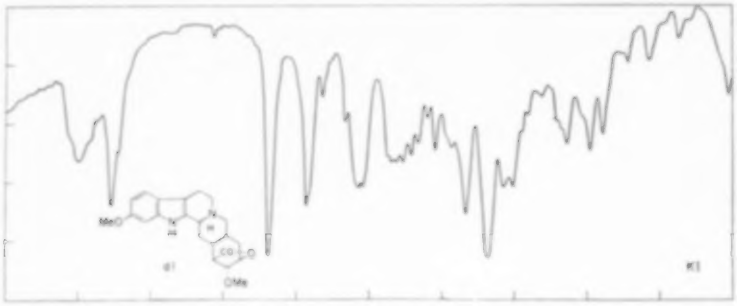
lactone was twice recrystallized from chloroform/ethyl acetate, m.p. (*vac.*) 245–246·5° (*dec.*).

Anal. Calcd. for $C_{22}H_{26}O_4N_2$: C, 69·09; H, 6·85; N, 7·33. Found: C, 68·98; H, 6·57; N, 7·39.

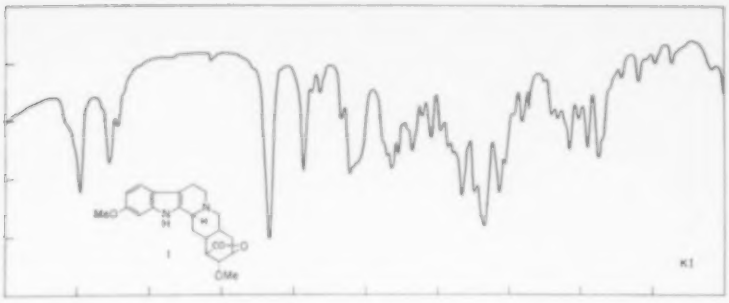


l Iso*reserpic acid hydrochloride*. *l* Methyl-O-acetyl-*iso*reserpate (200 mg) was dissolved in methanol (5 cm³) and 40 per cent aqueous potash (1·5 cm³), and boiled under nitrogen for 2 hr. The resulting solution was acidified to Congo with hydrochloric acid (1 : 1), and filtered from precipitated potassium chloride. The filtrate was concentrated to dryness, boiled with 10 cm³ of anhydrous methanol, and filtered again from potassium chloride. The filtrate was again concentrated to dryness. The residual solid was boiled with 10 cm³ of methanol and 2 cm³ of acetone, and filtered to remove a small amount of insoluble material. The filtrate was concentrated to about 5 cm³, and an equal volume of acetone was added. Colorless needles (131 mg) of the hydrochloride then separated. The mixture was cooled, the product was collected by filtration, the mother liquors were concentrated to about 2 cm³ and diluted with 5 cm³ of acetone to give a further 46 mg of product. The total yield of hydrochloride was 177 mg (92 per cent), m.p. (*vac.*) 273–274° (*dec.*). Further recrystallization from acetone/methanol gave colorless needles, m.p. (*vac.*) 278–279° (*dec.*).

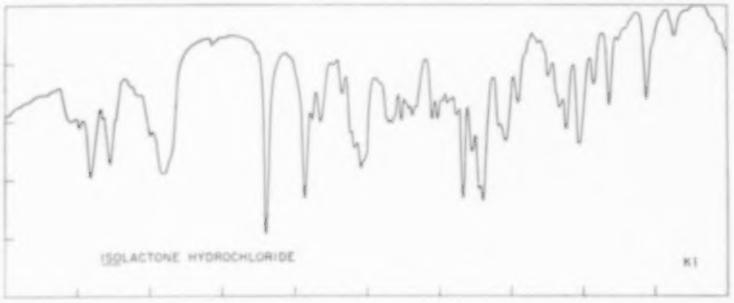
l Iso*reserpic acid lactone*(LXXVIII). *l Iso*reserpic acid hydrochloride (69 mg) and N,N′-dicyclohexylcarbodiimide (40 mg) in dry pyridine (4 cm³) were heated on the steam bath in an atmosphere of nitrogen for 1 hr; a precipitate separated from the reaction mixture. The mixture was allowed to stand at room temperature for 3 hr, and was then concentrated to 2 cm³, cooled, and filtered to give 82 mg of the *hydrochloride* of the *iso*lactone (LXXVIII) (see below), admixed with some di*cyclo*hexylurea. This solid mixture was added to 25 cm³ of chloroform and extracted three times with 1 N sulfuric acid. The combined acid fractions were washed with chloroform and then made basic with solid sodium carbonate. The basic solution was extracted three times with chloroform and the extract was dried over anhydrous sodium sulfate. The oily residue which remained after removal of the solvent crystallized when ethyl acetate was added. The crude product (31 mg) was recrystallized from chloroform/ethyl acetate to give 25 mg (41 per cent) of *l iso*reserpic acid lactone (LXXVIII), m.p. (*vac.*) 222·5–224° (*dec.*) ($[\alpha]_D^{24}$ − 138°, *c*, 1·05 ($CHCl_3$)).

Anal. Calcd. for $C_{22}H_{26}O_4N_2$: C, 69·09; H, 6·85; N, 7·33. Found: C, 69·17; H, 6·59; N, 7·30.

The infrared spectrum ($CHCl_3$) of the *laevo*rotatory *iso*lactone was found to be identical with that of the racemic *iso*lactone, whose preparation is described above.

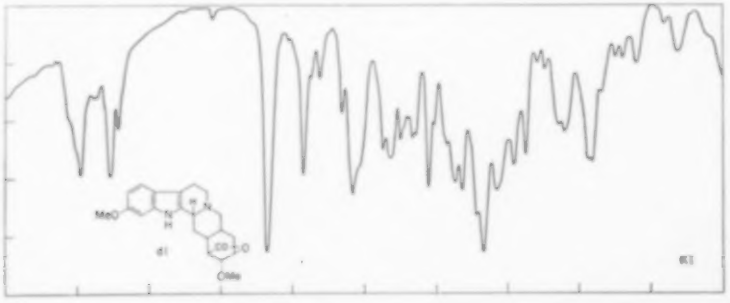


The *laevo*rotatory *iso*lactone forms a chloroform-soluble *hydrochloride*, which crystallizes in colorless needles, m.p. (*vac.*) 285–286° (*dec.*). It is this substance which separates directly from the reaction mixture, above.

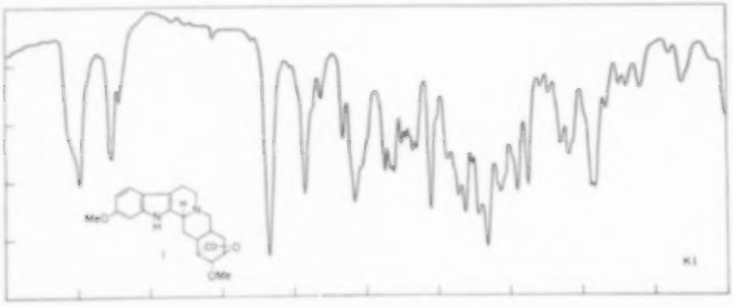


dl Reserpic acid lactone (LXXIX). *dl Iso*reserpic acid lactone (LXXVIII) (200 mg) was dissolved in 8 cm^3 of xylene containing 10 volume per cent of pivalic acid, and heated under reflux in an atmosphere of nitrogen for 16 hr. When the reaction mixture was cooled, 179 mg of crystalline material, m.p. (*vac.*) 280–281·5° (*dec.*) separated (perhaps the pivalate of the desired lactone). This material was collected, and the mother liquors were concentrated to yield a further 25 mg of the product. When the combined crystallizates were heated for some time at 140° in high vacuum, in order to effect complete removal of pivalic acid, 148 mg of the crude *lactone* (LXXIX) were obtained. When the lactone was recrystallized from dichloromethane/methanol, it separated as colorless needles, m.p. (*vac.*) 315–317° (*dec.*).

Anal. Calcd. for $C_{22}H_{26}O_4N_2$: C, 69·09; H, 6·85; N, 7·33. Found: C, 69·06; H, 6·86; N, 7·07.



l Reserpic acid lactone (LXXIX). A, *from l* isoreserpic acid lactone (LXXVIII). *l Iso*reserpic acid lactone (52 mg) in 2 cm^3 of xylene containing 10 volume per cent of pivalic acid was heated under reflux in an atmosphere of nitrogen for 13 hr. After some hours of boiling, the product started to crystallize from the boiling solution in long needles. At the end of the reaction time the solution was cooled, and 40 mg of crystalline material which had separated were collected and washed with benzene. The mother liquor was taken to dryness, treated with some drops of acetone, and allowed to crystallize. The combined crystals were dissolved in a small volume of chloroform/methanol (4 : 1), treated with an equal volume of benzene, and concentrated on the steam bath until crystallization commenced. Forty-one milligrams of *l* reserpic acid lactone (LXXIX), m.p. (*vac.*) 319–321° (*dec.*) were obtained as colorless needles. The mixture melting point (*vac.*) with reserpic acid lactone, prepared as described below (m.p. (*vac.*) 325–326° (*dec.*)) was 321–322° (*dec.*). The infrared spectra of the two samples were identical.



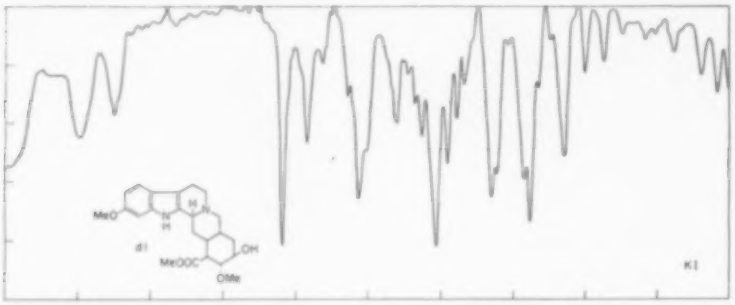
B, *from methyl reserpate* (LXXXI). Aluminium *iso*propoxide (204 mg) was dissolved in xylene (3 cm^3). Methyl reserpate (LXXXI) (55 mg) was added, and the reaction mixture was brought to boil. The ester went into solution readily, and after approximately 5 min, the lactone began to separate as colorless needles. The reaction mixture was heated under reflux for 2 hr. The product which had separated was removed by filtration and washed with xylene and ether; 46 mg (91 per cent) of reserpic acid lactone (LXXIX), m.p. (*vac.*) 325–326° (*dec.*) were obtained.

C, *from methyl-O-acetylreserpate*. Aluminium *iso*propoxide (170 mg) was dissolved in xylene (1·5 cm^3). Methyl-O-acetylreserpate (50 mg) was added, and the reaction mixture was brought to boil. The ester went into solution readily, and after 15 min the lactone began to separate in crystalline form. The reaction was allowed to proceed for 2 hr. The mixture was cooled, and the lactone which had separated was cooled and washed with xylene and ether; 40 mg. (95 per cent) of reserpic acid lactone (LXXIX), m.p. (*vac.*) 326–327° (*dec.*), were obtained as colorless needles.

D, *from reserpine*. Reserpine (4·1 g) was added to a solution of aluminium *iso*propoxide (10·5 g) in xylene (175 cm^3), and the resulting mixture was heated under reflux in an atmosphere of nitrogen. After 1 hr, the addition of a seed of reserpic acid lactone to the boiling solution initiated the separation of the product as colorless needles. After the reaction mixture had been kept under reflux for 5 hr, it was cooled, and 2·22 g (86 per cent) of crude lactone were collected, and washed with benzene and ether. One recrystallization from boiling chloroform gave the lactone (LXXIX) as colorless needles, m.p. (*vac.*) 327–328° (*dec.*).

dl Methyl reserpate (LXXXI). *dl* Reserpic acid lactone (LXXIX) (449 mg) was dissolved in 135 cm^3 of absolute methanol containing 190 mg of sodium methoxide. The resulting solution was heated under reflux in an atmosphere of nitrogen for 90 min. The cooled solution was acidified with 0·5 cm^3 of glacial acetic acid and concentrated to dryness *in vacuo*. The residue was dissolved in methylene dichloride, which was then washed once with water and twice with saturated brine. The organic layer was dried over anhydrous sodium sulfate, and evaporated. When the oily residue was crystallized from methanol/ether, 382 mg of *dl* methyl reserpate (LXXXI), m.p. (*vac.*) 236–237·5° (*dec.*), were obtained. On further crystallization from methanol/ether, and then from acetone, the melting point (*vac.*) was raised to 241–242° (*dec.*).

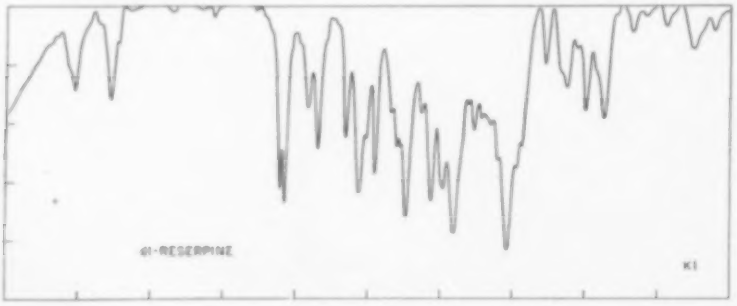
Anal. Calcd. for $C_{23}H_{30}O_5N_2$: C, 66·64; H, 7·30; N, 6·76. Found: C, 66·52; H, 7·36; N, 6·78.

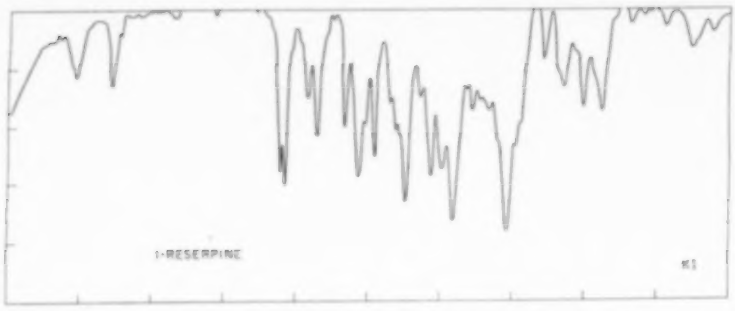


dl Reserpine (LXXXII). *dl* Methyl reserpate (50 mg) and 3,4,5-trimethoxybenzoyl chloride (150 mg, m.p. 80–81°) were dissolved in dry pyridine (1·5 cm^3) and the resulting solution was allowed to stand at room temperature in an atmosphere of nitrogen for four days. The pyridine was then removed *in vacuo* and the residue was dissolved in methylene chloride. The extract was washed twice with cold 1 N sodium carbonate solution, once with saturated brine, dried and evaporated to yield 183 mg of glassy residue. When this material was triturated with methanol/ether, 42 mg of crystalline *racemic reserpine* (LXXXII), m.p. (*vac.*) 258–259·5° (*dec.*) were obtained. For analysis the material was recrystallized twice from acetone/ether, m.p. (*vac.*) 260–262° (*dec.*).

Anal. Calcd. for $C_{30}H_{40}O_9N_2$: C, 65·11; H, 6·62; N, 4·60. Found: C, 65·01; H, 6·65; N, 4·12.

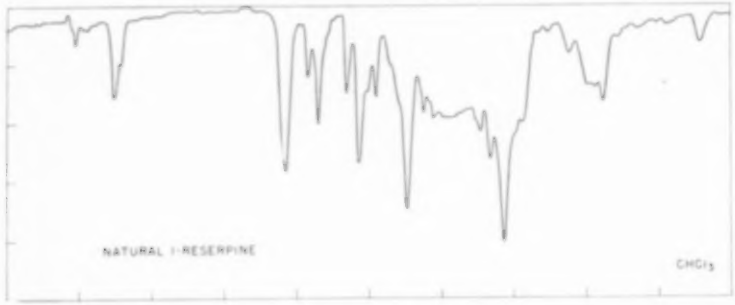
The infrared spectrum (KI!) of the racemic reserpine was found to be identical with that of natural *l* reserpine.

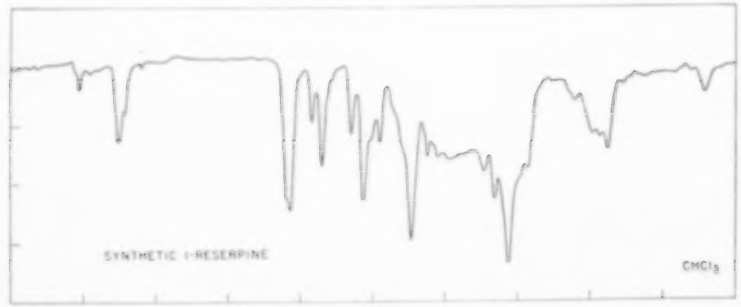


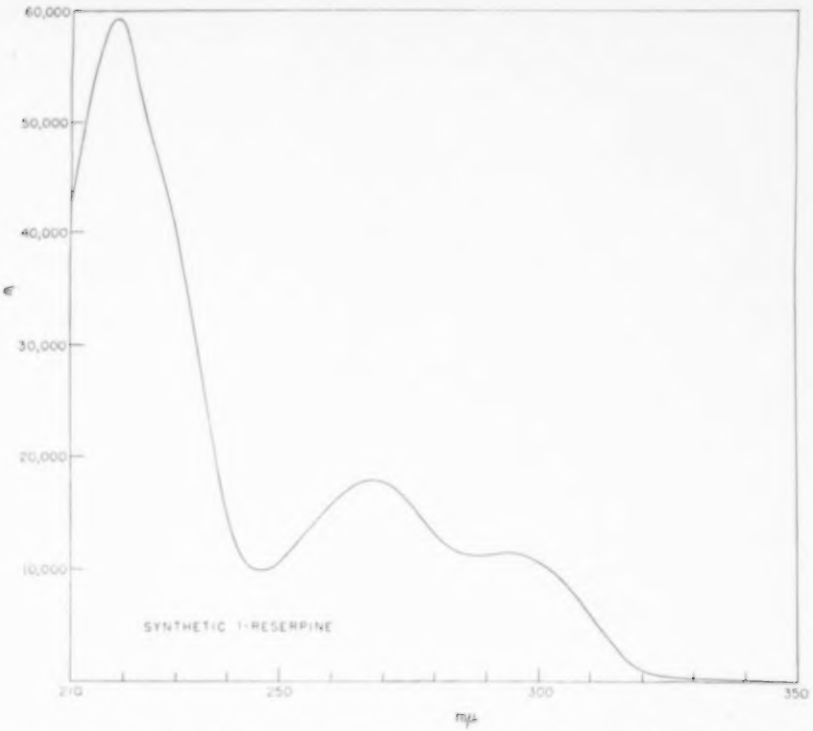


Resolution of racemic reserpine. Racemic reserpine (113 mg, m.p. (*vac.*) 260–262° (*dec.*)) was dissolved in methanol/chloroform (3 : 1). *d* Camphor-10-sulfonic acid (45 mg) was added. The solution was then concentrated on the steam bath to a small volume, and a seed of *l* reserpine-*d*-camphor-10-sulfonate was added. The colorless prisms (57 mg) which separated were recrystallized once from methanol. The beautifully crystalline prisms (52 mg) which separated were partitioned in the usual way between methylene chloride and ice-cold 1 N sodium hydroxide solution. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and taken to dryness *in vacuo*. The residue was crystallized twice from methylene chloride/methanol to give 28 mg of synthetic *l* reserpine (LXXXII) as beautiful colorless needles, m.p. (*vac.*) 286–288° (*dec.*) ($[\alpha]_D^{27}$ — 120°; *c*, 1·08 ($CHCl_3$)). The mixture melting point (*vac.*) with natural *l* reserpine (m.p. (*vac.*) 284–285° (*dec.*), $[\alpha]_D^{27}$ — 118°; *c*, 1·08 ($CHCl_3$)) was 285–286° (*dec.*).

The infrared and ultraviolet spectra of the synthetic and natural reserpines were found to be identical in all respects.







The residue obtained by evaporation of the mother liquors from the separation (above) of *l* reserpine-*d*-camphor-10-sulfonate were partitioned in the usual way between methylene chloride and ice-cold 1 N sodium hydroxide. The organic layer was washed with water and saturated brine, and dried over anhydrous sodium sulfate. It was then taken to dryness and the residual base was crystallized three times from methylene chloride. *d* Reserpine (26 mg) (m.p. (*vac.*) 281–284° (*dec.*), $[\alpha]_D^{25}$ + 117°; *c*, 0·86 ($CHCl_3$)) was obtained as colorless needles.

Acknowledgements—We are much indebted to Dr. Peter Bladon for his participation in the studies of the reaction of quinone with vinylacrylic acid and its ester.

Drs. Frank Hochstein (Pfizer), Norbert Neuss (Lilly) and Edmund Kornfeld (Lilly) very kindly provided us with natural reserpine, and a number of other useful materials.

Dr. Frederick Pilgrim and his associates (Pfizer, Groton) were most helpful in connection with the preparation of starting material on a large scale.

Dr. Stephen Nagy and his associates at the Microanalytical Laboratory of the Massachusetts Institute of Technology were most co-operative in connection with the many analytical problems which we faced.

Finally, we wish to express our warm appreciation of the generous financial support provided by Chas. Pfizer and Co., Inc.

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ALKALOID STUDIES*—XX

ISOLATION AND STRUCTURE OF TWO NEW CACTUS ALKALOIDS PILOCEREDINE AND LOPHOCERINE

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(*Received* 2 *August* 1957)

Abstract—A detailed examination of the alkaloids of the cactus *Lophocereus Schottii* has resulted in the isolation of two new alkaloids, piloceredine and lophocerine in addition to the previously described pilocereine; quaternary alkaloids were not encountered. Piloceredine ($C_{29}H_{44}N_2O_4$) was shown to be diastereoisomeric with pilocereine and potassium-liquid ammonia cleavage of its methyl and ethyl ethers yielded the same cleavage products as the corresponding derivatives of pilocereine. Lophocerine was obtained in impure form from the phenolic alkaloid fraction and is assigned the structure 1-*iso*butyl-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydro*iso*quinoline since upon methylation it afforded the known 1-*iso*butyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydro*iso*quinoline. Lophocerine appears to be the biogenetic precursor of pilocereine and piloceredine.

AS POINTED out in an earlier paper[1] dealing with the structure elucidation of pilocereine (Ia) this cactus alkaloid is of unusual interest since its empirical formula $C_{30}H_{44}N_2O_4$ differs markedly from those (less than 13 carbon atoms) of the other alkaloids found among the *Cactaceae*.[2] Consequently an effort was made to isolate additional alkaloids from the cactus *Lophocereus Schottii* which appeared to be the richest source[3] of pilocereine.

The pilocereine-depleted "non-phenolic" alkaloid fraction was subjected to chromatography and after the separation of an additional quantity of pilocereine a second alkaloid was isolated (m.p. 165–166°) the analysis of which ($C_{30}H_{44}N_2O_4$ with two methoxyl and two N-methyl groups) coincided with that of pilocereine (Ia). The infra-red spectrum of this alkaloid was identical with that of pilocereine (m.p. 175–176°) when measured in chloroform solution but appreciable differences were noticed when the spectra were determined in nujol mull. Furthermore, the X-ray diffraction patterns§ were different. The possibility of polymorphism was excluded in the following manner: (a) the new alkaloid—piloceredine—could be separated chromatographically from pilocereine; (b) the two alkaloids exhibited a marked

* Part XIX by M. Gorman, J. P. Kutney, P. J. Scheuer, N. Neuss and C. Djerassi *Tetrahedron* **1** (1957) is in the press.

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‡ Postdoctorate research fellow, 1955–1956. Present address, Department of Chemistry, University of Connecticut, Storrs, Conn.

§ Kindly measured by Miss Ann Van Camp in the Eli Lilly Research Laboratories (Indianapolis, Indiana) through the courtesy of Dr. R. G. Jones.

[1] C. Djerassi, S. K. Figdor, J. M. Bobbitt and F. X. Markley *J. Amer. Chem. Soc.* **79**, 2203 (1957).

[2] For review see L. Reti in R. H. F. Manske and H. L. Holmes *The Alkaloids* Vol. IV, pp. 7–28, Academic Press, New York (1954).

[3] (a) G. Heyl *Arch. Pharm.* **239**, 451 (1901); (b) C. Djerassi, N. Frick and L. E. Geller *J. Amer. Chem. Soc.* **75**, 3632 (1953); (c) C. Djerassi, C. R. Smith, S. P. Marfey, R. N. McDonald, A. J. Lemin, S. K. Figdor and H. Estrada *Ibid.* **76**, 3215 (1954).

depression in melting point when mixed; (c) the two substances were not interconvertible by cross seeding in the same solvent; (d) as shown in Table 1, out of four derivatives, three exhibited very similar melting points but in each instance a marked mixture melting point depression was observed; (e) the respective acetates had very different melting points but even here the infra-red spectra were essentially identical when measured in carbon disulfide solution.

TABLE 1. COMPARISON OF MELTING POINTS OF PILOCEREINE, PILOCEREDINE AND DERIVATIVES

Derivative	Pilocereine*	Piloceredine
Free base	175–176°	165–166°
Diperchlorate	216–217°	221–222°
Acetate	186–186.5°	133–134°
Methyl ether	133–134° and 153–155°	141–142°
Ethyl ether	147–148°	150–152°

* These constants were determined simultaneously with those of piloceredine and in some cases differ very slightly from those reported earlier.[1,3b]

Piloceredine, like pilocereine, was optically inactive* and the similarities in physical properties suggest that the former might be the possible diastereoisomer of pilocereine (Ia). In order to confirm this supposition the appropriate ethers† of piloceredine were subjected to cleavage with potassium in liquid ammonia at −60° since identical products[4] should be obtained and indeed this proved to be the case. From the non-phenolic fraction of the ether cleavage of piloceredine methyl ether (Ib) there was isolated 1-*iso*butyl-2-methyl-6-methoxy-1,2,3,4-tetrahydro*iso*quinoline (IIa), 1-*iso*butyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydro*iso*quinoline (IIc) and 1-*iso*butyl-2-methyl-6,7-dimethoxy-8-hydroxy-1,2,3,4-tetrahydro*iso*quinoline (IIIa). Methylation of the phenolic cleavage products followed by chromatography afforded 1-*iso*butyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydro*iso*quinoline (IIc) and 1-*iso*butyl-2-methyl-6,7,8-trimethoxy-1,2,3,4-tetrahydro*iso*quinoline (IIIb). The identification of these products establishes structure (Ib) for piloceredine methyl ether. In order to prove rigorously the position of the kryptophenolic hydroxyl group in the free alkaloid, a sample of piloceredine ethyl ether (Ic) was treated with potassium in liquid ammonia at −60° and 1-*iso*butyl-2-methyl-6-methoxy-7-ethoxy-1,2,3,4-tetrahydro*iso*quinoline (IId) was identified among the cleavage products. The isolation of (IId) *ipso facto* locates the free hydroxyl group of piloceredine; thus it follows that this alkaloid possesses the same structure (Ia) as pilocereine and that both possible diastereoisomers occur in the same cactus.

It has already been mentioned above that both alkaloids were optically inactive. With the information at hand it is impossible to say whether pilocereine and

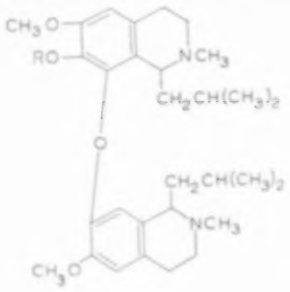
* Established by examination in a spectropolarimeter down to 350 mμ.[3]

† It has been noted in the case of pilocereine that ether cleavage of the base itself is accompanied by skeletal rearrangement.[1]

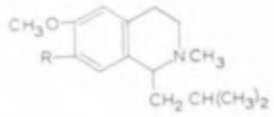
[4] The synthesis of the relevant methoxy and ethoxy tetrahydro*iso*quinolines has already been recorded by C. Djerassi, F. X. Markley and R. Ehrlich *J. Org. Chem.* **21**, 975 (1956).

piloceredine exist as racemates in the cactus or whether racemization occurred during the isolation procedure. Späth and Kesztler[5] have observed that resolved, synthetic pellotine (IV) racemizes quite readily. In order to determine whether this also applies to pilocereine and piloceredine a variety of unsuccessful resolutions were attempted as outlined in the experimental section.

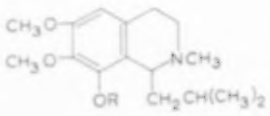
Of the total alkaloids of the cactus *Lophocereus Schottii* approximately 5 per cent is soluble in alkali. The phenolic alkaloids could not be purified but when a distilled portion was methylated with diazomethane and subjected to careful chromatography there was isolated—as the picrate—a small amount of 1-*iso*butyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydro*iso*quinoline (IIc). Consequently, this substance must represent the methyl ether of another alkaloid—now named lophocerine—and we are suggesting structure IIb (1-*iso*butyl-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydro*iso*quinoline) for it, although it is appreciated that the position of the free phenolic group(s) follows only from analogy.* We consider the isolation of lophocerine (IIb) to be of some biogenetic significance since both monomeric (IIb) and dimeric (Ia) fragments are found in the same cactus. It is very likely that pilocereine and piloceredine are produced by phenol coupling and lophocerine (IIb) contains all of the requisite structural features[6] for such a biosynthetic step.



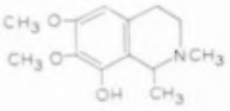
I a R=H
b R=CH_3
c R=C_2H_5
d R=CH_3CO



II a R=H
b R=OH
c R=OCH_3
d R=OC_2H_5



III a R=H
b R=CH_3



IV

* The structure would have been proved rigorously if the ethylation product could have been isolated in pure form but this did not prove to be the case. Our failure is probably due to the fact that only a small portion of the phenolic fraction is represented by lophocerine—most of it being polymeric material—and the expected 1-*iso*butyl-2-methyl-6-methoxy-7-ethoxy-1,2,3,4-tetrahydro*iso*quinoline picrate crystallizes only with difficulty if not completely pure.

[5] E. Späth and F. Kesztler *Ber. Dtsch. Chem. Ges.* **69**, 755 (1936).
[6] R. Robinson *The Structural Relations of Natural Products* p. 85, Oxford University Press (1955); R. H. F. Manske *The Alkaloids* Vol. IV, p. 1, Academic Press, New York (1954).

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EXPERIMENTAL*

Isolation of piloceredine (Ia).† A 5·5 kg portion of dried alcoholic extract derived from 36 kg of dry *Lophocereus Schottii* was partitioned between ether and 10 per cent hydrochloric acid, any insoluble material being discarded. The combined acid solutions were basified to pH 9 with ammonium hydroxide which caused the separation of some black gum. After thorough extraction with ether and filtration of any insoluble material the aqueous layer was examined for quaternary salts by addition of ammonium reineckate. The precipitate was converted into the sulfate, chloride and picrate but no evidence for the presence of quaternary salts could be found. Typical experimental procedure is already on record.[7]

The ether layer was washed with 5 per cent sodium hydroxide solution and this was processed separately (see below) for phenolic alkaloids. Concentration of the ether solution to a small volume and chilling in the refrigerator for several days furnished 220 g of substantially pure pilocereine which exhibited m.p. 175–176° after one recrystallization from acetone-hexane.

The oily mother liquor was passed in benzene solution over 7 kg of alumina (deactivated with 210 cm^3 of 10 per cent acetic acid) and the benzene and ether fractions were combined and rechromatographed on 7·5 kg of activated alumina (activity I-II). Development was effected with benzene, benzene-ether and ether and 6 fractions of 2·5 l. each were collected. Fraction 1 (elution with benzene) yielded 13·9 g of a mixture (m.p. 151–161°) of pilocereine and piloceredine which was resolved by repeated chromatography into 3·0 g of pilocereine and 9·5 g of piloceredine. Fractions 2–6 yielded 80·1 g of *piloceredine*, m.p. 161–163°, raised to m.p. 165–166° after recrystallization from acetone. A mixture with pilocereine melted at 153–173° and the two substances could not be interconverted by cross seeding. The infra-red spectra in chloroform and in carbon disulfide were identical, but substantial differences were noted in a nujol infra-red spectrum and in the X-ray diffraction patterns.

Anal. Calcd. for $C_{30}H_{44}N_2O_4$: C, 72·54; H, 8·93; N, 5·64; O, 12·89; 2 methoxyl, 12·49; 2 N—CH_3, 6·05. Found: C, 72·61; H, 8·51; N, 5·59; O, 12·95; methoxyl, 12·30; N—CH_3, 6·89.

Piloceredine diperchlorate. A solution of piloceredine in dilute hydrochloric acid was treated with aqueous ammonium perchlorate and the resulting precipitate was recrystallized from methanol, m.p. 221–222°, depressed to 210–213° upon admixture with pilocereine diperchlorate (m.p. 216–217°). The finger print regions of the respective nujol mull infra-red spectra were different. The analytical sample was dried at 130° and 4 mm for 24 hr.

Anal. Calcd. for $C_{30}H_{44}N_2O_4 \cdot 2\,HClO_4$: C, 51·64; H, 6·64; N, 4·01; O, 27·52; Cl, 10·10. Found: C, 51·31; H, 6·88; N, 4·32; O, 27·25; Cl, 9·99.

Piloceredine acetate (Id). A sample of piloceredine was acetylated with acetic anhydride and pyridine and all volatile material was removed *in vacuo*. The residue was taken up in ether, washed with potassium carbonate solution, dried, evaporated

* Melting points are uncorrected. The microanalyses were carried out by Dr. A. Bernhardt, Mülheim, Germany.

† We are indebted to Parke, Davis and Co., Detroit, Michigan for putting the facilities of their pilot plant at our disposal.

[7] M. Tomita and T. Nakano *J. Pharm. Soc. Japan* **72**, 727 (1952).

and chromatographed on deactivated alumina. Elution with benzene and recrystallization from petroleum ether afforded the crystalline acetate, m.p. 133–134°, depressed to 120–128° upon admixture with pilocereine acetate (m.p. 186°); the infra-red spectra of the two samples, measured in carbon disulfide were practically identical.

Anal. Calcd. for $C_{32}H_{46}N_2O_5$: C, 71·34; H, 8·61; N, 5·20; O, 14·85. Found: C, 71·35; H, 8·63; N, 5·34; O, 14·57.

Cleavage of piloceredine methyl ether (Ib). A solution of 4·5 g of piloceredine in 100 cm³ of methanol was treated for 4 days at 0° with distilled ethereal diazomethane (from 10 g of N-nitroso methylurea) and then for a further 6 days with a fresh portion of diazomethane. After evaporation to dryness the residue was recrystallized several times from hexane whereupon the methyl ether (Ib) exhibited m.p. 141–142°. A mixture melting point with pilocereine methyl ether (m.p. 133–134°) was depressed to 124–130°. The infra-red spectra showed marked differences in nujol mull but were essentially identical when measured in chloroform solution.

Anal. Calcd. for $C_{31}H_{46}N_2O_4$: C, 72·90; H, 9·08; N, 5·49; O, 12·53. Found: C, 73·27; H, 8·98; N, 5·40; O, 12·54.

The ether cleavage was accomplished by adding 3·4 g of potassium metal with stirring at −60° to 2·5 g of piloceredine methyl ether (Ib) in 100 cm³ of ether and 500 cm³ of distilled liquid ammonia. After 7 hr ammonium chloride was added to discharge the blue color and the ammonia was allowed to evaporate overnight. The residue was partitioned between ether and 3 per cent sodium hydroxide solution, the organic phase was extracted with dilute hydrochloric acid and basified with ammonium hydroxide and the non-phenolic basic fraction (1·68 g) was re-extracted with ether. Separation was effected by chromatographing this material on 140 g of alumina deactivated with 4·2 cm³ of 10 per cent acetic acid and collecting about 50 fractions.

Fractions 20–25 eluted with benzene furnished—after treatment with picric acid—0·51 g of 1-iso*butyl*-2-*methyl*-6-*methoxy*-1,2,3,4-*tetrahydro*isoquinoline (IIa) *picrate* m.p. 152–153°. Fractions 27–33 (1 : 1 benzene-ether) yielded 0·5 g of 1-iso*butyl*-2-*methyl*-6,7-*dimethoxy*-1,2,3,4-*tetrahydro*isoquinoline (IIc) *picrate* m.p. 183–184° while the ether eluates (fractions 39–43) after conversion to the picrate led to 0·14 g of 1-iso*butyl*-2-*methyl*-6,7-*dimethoxy*-8-*hydroxy*-1,2,3,4-*tetrahydro*isoquinoline (IIIa) *picrate* m.p. 152–153°.

The original 3 per cent sodium hydroxide extracts were made acid with hydrochloric acid, washed with ether (discarded), made alkaline with ammonium hydroxide and extracted with ether. Evaporation of the ether gave 0·72 g of phenolic, basic oil which was methylated in ether-methanol solution for 8 days at 0°. When the methylated phenolic fraction was chromatographed in the above described manner and the various eluates treated with picric acid there was obtained 0·46 g of 1-iso*butyl*-2-*methyl*-6,7-*dimethoxy*-1,2,3,4-*tetrahydro*isoquinoline (IIc) *picrate* m.p. 181–184° and 0·18 g of 1-iso*butyl*-2-*methyl*-6,7,8-*trimethoxy*-1,2,3,4-*tetrahydro*isoquinoline (IIIb) *picrate* m.p. 132–134°. Identification was accomplished in each case by mixture melting point determinations with authentic samples.[1,4,5]

Cleavage of piloceredine ethyl ether (Ic). Piloceredine (6·0 g) was converted into its ethyl ether (6·06 g, m.p. 147–149°) with diazoethane exactly as described above for

[5] C. Djerassi, J. J. Beereboom, S. P. Marfey and S. K. Figdor *J. Amer. Chem. Soc.* **77**, 484 (1955).

the diazomethane methylation except that absolute ethanol was used as solvent. The analytical sample obtained from hexane showed m.p. 150–152°, depressed to 133–141° upon admixture with pilocereine ethyl ether (m.p. 147–148°). The infra-red spectra of the two ethers in chloroform solution were identical but differed in the finger print region when measured in nujol mull.

Anal. Calcd. for $C_{32}H_{48}N_2O_4$: C, 73·24; H, 9·22; N, 5·34; O, 12·20; 2 N—CH_3, 5·72. Found: C, 73·32; H, 9·20; N, 5·20; O, 12·43; N—CH_3, 6·09.

The cleavage of 2·5 g of the ethyl ether was conducted as described above for the methyl ether except that the reaction time was extended to 24 hr. From the non-phenolic portion there was isolated after chromatography and conversion to the picrate 0·31 g of 1-iso*butyl*-2-*methyl*-6-*methoxy*-7-*ethoxy*-1,2,3,4-*tetrahydroisoquinoline* (IId) *picrate* m.p. 149–150° which was not depressed on mixture with a synthetic specimen.[4]

Lophocerine (IIb). A portion of the phenolic alkaloids (*c.* 5 per cent of the total alkaloids) was distilled and 0·53 g of material distilling between 150–225° at 0·05 mm was methylated with diazomethane in methanol-ether for 3 days. After washing with alkali and acid, basifying the acid extracts and taking up in ether, evaporation of the dried organic phase gave 0·26 g of oil which was chromatographed on 20 g of alumina deactivated with 0·6 cm^3 of 10 per cent acetic acid. Elution with hexane-benzene (1 : 2), conversion to the picrate and recrystallization from ethanol yielded 80 mg of 1-iso*butyl*-2-*methyl*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* (IIc) *picrate* m.p. 185–186°, undepressed when mixed with a synthetic sample.[8]

Attempted resolutions. The resolution of pilocereine was attempted with the following reagents without success: D-tartaric acid, L-dibenzoyltartaric acid, D-camphoric acid, D-10-camphorsulfonic acid, D-quinic acid, L-malic acid, N-acetyl-L-leucine and (+)-N-acetyl-threo-β-phenyl-l-serine (kindly provided by Dr. A. Fürst, Hoffmann-LaRoche, Basel).

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THE CONFORMERS OF 2-BROMO*CYCLO*HEXANONE

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Abstract—The infrared and ultraviolet carbonyl absorptions of 2-bromo*cyclo*hexanone have been examined in a variety of solvents. The data are consistent with an equilibrium *axial*-2-bromo*cyclo*hexanone ⇌ *equatorial*-2-bromo*cyclo*hexanone for which the equilibrium constant varies as a function of solvent over the range 0·3–1·0. The earlier and apparently contradictory data in the literature have been re-examined and are considered to be consistent with this conclusion.

CONFORMATIONAL analysis of 2-bromo*cyclo*hexanone (I) suggests that either the axial or the equatorial conformation would be possible for the 2-bromine substitutent. Accordingly, an equilibrium mixture of *axial*-(Ia) and *equatorial*-2-bromo*cyclo*hexanone (Ie) might be expected to exist. A simpler situation could occur if one conformation for the bromine (axial or equatorial) were much preferred and I would then be essentially conformationally pure. The following data were interpreted by Corey[1] as evidence that 2-bromo*cyclo*hexanone (I) had almost exclusively the axial conformation for the bromine. First, the main infra-red carbonyl absorption maximum of I (carbon tetrachloride solution) was only sightly displaced from that of *cyclo*hexanone (II), a fact which indicated the presence of the axial conformer.[2] A shoulder on the main absorption band which occurred at 14 cm^{-1} higher frequency relative to II was assigned[2] to the conformer which had the bromine equatorial, but the slight intensity of the shoulder was considered to indicate that only a "small amount" of the *equatorial* isomer Ie was present. Second, support for the conclusions drawn from the infrared spectra was obtained when a theoretical value for the "minimum" energy difference between the two conformations was calculated. The magnitude of this energy difference predicted an equilibrium mixture that contained "at least 97 per cent" of *axial*-2-bromo*cyclo*hexanone.

The dipole moment of I in heptane, benzene and dioxane solution was determined by Kumler and Huitric.[3] In the light of Corey's work, and especially the energy calculations, the experimentally determined moment of I in all solvents would be expected to be virtually identical with the theoretical dipole moment calculated for Ia. It was found, however, that the dipole moment of I increased with increasing dielectric character of the solvent employed for the measurement and was of such a magnitude in each medium as to indicate far less than the estimated[1] 97 per cent of Ia to be present. These data might have been interpreted as consistent with an equilibrium mixture of Ia and Ie which was influenced by the solvent but, because of Corey's work, Kumler and Huitric preferred to consider that a third isomer, a "flexible form" whose conformation was intermediate between Ia and Ie, was present.

[1] E. J. Corey *J. Amer. Chem. Soc.* **75**, 2301 (1953).
[2] R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner *Ibid.* **74**, 2828 (1952).
[3] W. D. Kumler and A. C. Huitric *Ibid.* **78**, 3369 (1956).

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The two investigations which have ascribed very different conformational situations for 2-bromo*cyclo*hexanone (I) employed different physical quantities to describe the system I. To correlate the earlier data and to provide a starting point for the present study it was necessary to choose the most reasonable individual bond moments for the carbon-bromine and carbon-oxygen dipoles of I and to determine the dipole angles of Ia and Ie as precisely as possible. These two sets of constants were necessary for the calculations of the theoretical dipole moments of Ia and Ie and of the energy difference between the two conformers. Corey deliberately chose physical constants which would yield a minimum energy difference,[1] and it should be noted that estimates of the individual bond moments and of the dipole angles as well as a simple method by which the geometry of I could be calculated were not then available. Kumler and Huitric[3] assigned the individual bond moments from consideration of related studies, but apparently calculated dipole angles for Ia and Ie on the basis of a geometrically inadequate model.

A more accurate representation of the structure of I than was used by the previous workers is now available, for Corey and Sneen[4] have determined by vector analysis the exact geometry of "*cyclo*hexylidene" (chair form). With a simple correction to replace the exocyclic methylene carbon by oxygen, this geometry allowed exact calculation of the molecular geometry of *cyclo*hexanone (II) and thus of the system I.* The dipole angles (χ) of 109°51′and 51°54′ and the dihedral angles (ϕ) of 102°13′ and 16°17′ were determined for Ia and Ie, respectively.[5] The geometry of the two conformations is summarized in Figure 1.

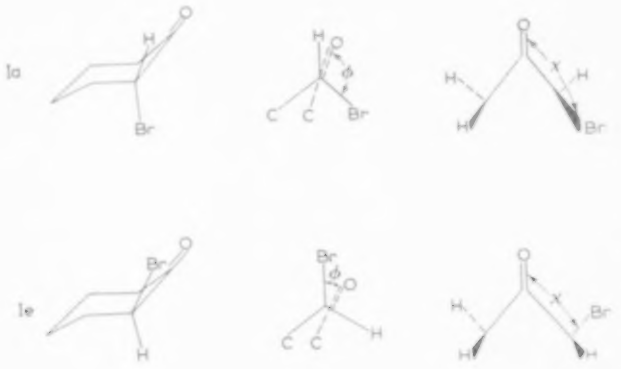

FIG. 1.

The dipole moments determined for *cyclo*hexyl bromide and *cyclo*hexanone (II) were 2·1 D[6] and 2·9 D[7], respectively. As evidenced by work with other compounds wherein rigid models were employed to describe a molecule,[8] the values determined

* Since the necessary data are not available, the model here assumed does not take into account the probable slight spreading of the angles by dipole-dipole repulsions.

[4] E. J. Corey and R. A. Sneen *J. Amer. Chem. Soc.* **77**, 2505 (1955).
[5] R. C. Cookson *J. Chem. Soc.* 282 (1954) estimated dihedral angles of 105° and 15° with no indication as to the methods employed to obtain these values.
[6] O. Hassel and E. Naeshagen *Z. Physik. Chem.* B **15**, 373 (1932).
[7] R. J. W. LeFevre *Dipole Moments* p. 63. John Wiley, New York (1953).
[8] P. Bender, D. L. Flowers and H. L. Goering *J. Amer. Chem. Soc.* **77**, 3463 (1955).

for the simple cases will not describe the existing individual bond moments of the carbon-halogen and carbon-oxygen dipoles of a molecule such as I because inductive interaction between adjacent dipoles operates to lower the actual bond moment of each dipole. The adjusted values of 1·91 D (μ_{C-Br}) and 2·83 D ($\mu_{C=O}$) were selected by Kumler and Huitric by analogy with other data[8] as the best values for the case at hand and the present study employs these bond moments for each conformer also.* Table 1 summarizes the physical quantities which are to be utilized in the present discussion and compares them with the values of the two previous investigations.

Theoretical energy calculations. The total energy difference between Ia and Ie is the net result of a steric and an electrostatic energy unique to each conformer. Equation (1) was employed by Corey[1] to calculate the electrostatic energies, E_e, of Ia and Ie, and this equation was originally derived for two (magnetic) dipoles interacting in

$$E_e = \frac{\mu_{C-Br}\mu_{C=O}}{r^3} \quad (\cos\chi - 3\cos\alpha_1 \cos\alpha_2) \qquad (1)$$

a field of constant force (vacuum, dielectric constant unity).[9] However, in a molecule in a liquid phase the effective dielectric constant D in the vicinity of the dipoles is certainly not unity. Thus the electrostatic energies calculated from equation (1) must be divided by the dielectric constant of the medium through which the dipoles interact.† Although no way is available to precisely calculate this term an approximation to a similar situation was suggested by Kirkwood and Westheimer.[10] A molecule which contained interacting charges was considered to outline a sphere inside which the charges were placed and the effective dielectric constant within this sphere was proposed to have the value 2, this value being considered more reasonable than unity. The sphere was then considered to be surrounded by a medium having a dielectric constant equal to that of the solvent. This approximation enabled the cited authors to obtain calculated values for dissociation constants of various substituted organic acids which were in good agreement with experiment, and their success would seem to justify the use of this concept of a local dielectric constant for the present study. If the value 2 is taken to represent the dielectric constant of the medium within the molecule, and if this molecule is placed in a bulk medium of dielectric constant 2 (heptane solution), then the electrostatic energies calculated for Ia and Ie may be more reasonably expected to approximate the real situation.

The steric energy difference of Ia and Ie is difficult to assess for there are few pertinent data which permit calculation of this term. Corey[1] estimated 0·4 kcal/mole for this difference, the energy of Ia being more positive, and this value was retained for the present calculations.

Employing the physical quantities developed in the present study for system I (Table 1) and equation (1) divided by the dielectric constant 2, the difference in electrostatic energy between Ia and Ie in heptane solution was calculated to be 1·93

* Since Ia and Ie have quite different dipole angles, the mutual inductance of the adjacent dipoles may be slightly different for each conformer. As a result, the actual individual bond moments of Ia may be larger and those of Ie are possibly smaller.[8] Further refinement of these constants is not readily accomplished and would in any event provide only a minor change in the calculated dipole moments of each conformer.

† This relationship follows from classical electrostatics which shows that the interaction energy of charges in a medium is equal to the energy in vacuum divided by the dielectric constant of the medium.

[9] J. H. Jeans *Mathematical Theory of Electricity and Magnetism* (5th Ed.) p. 377. The University Press, Cambridge (1933).

[10] J. G. Kirkwood and F. H. Westheimer *J. Chem. Phys.* **6**, 506, 513 (1938).

TABLE 1

Conformer	Dipole angles	μ_{C-Br}	$\mu_{C=O}$	Investigation
Ia	109°51′	1·91 D	2·83 D	This study
Ie	51°54′			
Ia	125°	1·91 D	2·83 D	Kumler and Huitric[3]
Ie	55°			
Ia	134°	1·2 D	2·5 D	Corey[1]
Ie	50°			

kcal/mole, the Ia conformer being the more stable. The steric energy of 0·4 kcal/mole which destabilizes Ia provided a total energy difference of 1·53 kcal/mole; this energy difference indicates an equilibrium mixture comprised of 93 per cent Ia and 7 per cent Ie for heptane solution at 25°. The dipole moment data[3] are consistent with an equilibrium mixture in heptane solution which contains 68 per cent Ia and 32 per cent Ie (Table 2). In view of the approximations required for the energy calculations, the

TABLE 2.—CARBONYL ABSORPTION DATA OF I AND II IN VARIOUS SOLVENTS

No.	Solvent	λ_{max} cm^{-1}			Molarity I and II	Optical densities		% I as Ia infrared	% I as Ia dipole moments[a]
		Ie	Ia	II		Ia	II		
1	Homogeneous	1749	1732	1724	—	—	—	c. 50[b]	—
2	Carbon tetrachloride	1742	1730	1730	0·126	0·330	0·447	74	
3	Chloroform	1736	1721	1711	0·120	0·348	0·500	68	
4	Carbon disulfide	1738	1726	1726	0·137	0·348	0·509	68	
5	Benzene	1741	1729	1724	0·127	0·300	0·491	60	60
6	Dioxane	1740	1728	1719	0·119	0·259	0·457	57	51
7	Dimethyl sulfoxide	1743	1729	1717	0·133	0·260	0·494	53	
8	*n*-Heptane	1741	1728	1732	0·122	0·232	0·516	45[b]	68
9	Cyclohexane	1743	1728	1737	0·130	0·297	0·544	55[b]	

[a] Calculated with the theoretical dipole moments $\mu_{Ia} = 2{\cdot}82$ D, $\mu_{Ie} = 4{\cdot}34$ D, obtained employing the constants of the present study (Table 1), and the equation[17] $\mu^2_{observed} = N_a\mu^2_{Ia} + N_e\mu^2_{Ie}$

[b] See text for discussion concerning these apparently anomalous values.

agreement with the dipole moment studies is reasonable. Of more significance is the qualitative conclusion to be derived from these calculations that an equilibrium mixture of Ia and Ie may be expected to exist in which the minor conformer is present to the extent of *at least* several per cent.

For interconvertible isomers of different electrostatic energies, the composition of their equilibrium mixture is influenced by the solvent in which the measurement is made.[11] For the system I, conformer Ie has the higher electrostatic energy. Accordingly the position of the predicted Ia $\rightleftarrows$ Ie equilibrium would be expected to be displaced to the right in solvents of higher dielectric constant than heptane. This shift

[11] K. Kozima, K. Sakashita and S. Maeda *J. Amer. Chem. Soc.* **76**, 1965 (1954); A. Tulinskis, A. DiGiacomo and C. P. Smyth *Ibid.* **75**, 3552 (1953).

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is exactly what has been found from the dipole moment study of I in various solvents[3] and from the spectral studies of the present investigation.

Spectral studies. The infrared and ultraviolet absorption curves of I and II were examined in various solvents, and these spectral studies suggest an observable equilibrium.* The infrared data obtained for each solvent allowed an estimation of the position of the equilibrium for the particular medium and the ratio of *axial* to *equatorial* conformer was obviously influenced by the solvent.

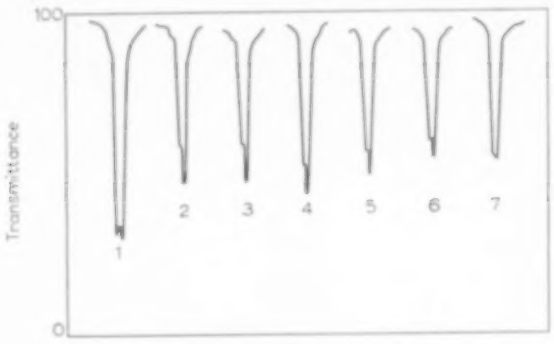

FIG. 2. Carbonyl absorption bands of 2-bromo*cyclo*hexanone in various solvents. The band numbers correspond to those described in Table 2.

The infrared carbonyl absorptions of 2-bromo*cyclo*hexanone (I) and cyclohexanone (II) in the solvents chloroform, carbon disulfide, carbon tetrachloride, *n*-heptane, *cyclo*hexane, benzene, dioxane, and dimethyl sulfoxide were compared at similar molar concentrations and the curve of I in each of these solvents was composed of two maxima which could not be completely resolved, as is shown in Fig. 2. The absorption band which was displaced to a higher frequency from the maximum of *cyclo*hexanone was assigned to Ie and the absorption band which was at a similar frequency to that of II was assigned to Ia.[2] Table 2 records the carbonyl frequencies.

Analysis of the infrared spectra to determine the amounts of Ia and Ie present in the various solutions was complicated by the fact that the conformers cannot be obtained in pure form and the absorption curves of Ia and Ie were not cleanly separable. However, an *axial* α-bromoketosteroid has an integrated carbonyl absorption intensity virtually identical with the similar area calculated for the parent ketosteroid.[2] This relationship suggested that the ratio of extinction coefficients of the Ia and II maxima would serve to estimate the per cent of Ia present in the various solutions, and this simplifying approximation was employed for the present study. The amount of Ie present was taken to be the difference between 100 per cent and the estimated per cent of Ia. An alternative method of curve resolution is to reflect the side of the principle band (extinction coefficient plotted against frequency) away from the interfering band about its axis and to graphically integrate separately the symmetrical band

* Certain aliphatic α-halocarbonyl compounds exist as a mixture of rotational isomers and the presence of these isomers has been confirmed from the infrared spectra. L. J. Bellamy, L. C. Thomas and R. L. Williams [*J. Chem. Soc.* 3704 (1956)], studied the infrared spectra of some *o*-chloroacetophenones at different temperatures, and each of these compounds had two carbonyl absorption bands which were not completely resolvable. From the manner in which the relative intensities of the maxima were influenced by temperature, assignment of each of the carbonyl absorption bands to a particular rotational isomer was possible.

and the absorption outside the symmetrical band.[12] This procedure is carried out with difficulty with spectra obtained on the Baird instrument because the areas are so small. This admittedly inaccurate method was also applied in the present case, and the areas of the curves so obtained (assuming the same inherent integrated band intensities) indicated, for example, 80 per cent and 73 per cent Ia in chloroform and benzene, respectively. Since the equatorial band is probably in fact of lower inherent intensity,[2] these would be minimum values, and they certainly are in as good agreement with the more accurate values found from the extinction coefficients as can be expected.

For the solvents carbon tetrachloride, chloroform, carbon disulfide, benzene and dioxane, the carbonyl absorption curve had a main band (Ia isomer) with a shoulder on the higher frequency side (Ie isomer) and the amounts of Ia present in these solutions varied in a regular manner from 74–57 per cent (Table 2). Dimethyl sulfoxide ($D \simeq 45$) solutions of I afforded an absorption curve having two non-resolvable bands of nearly equal intensity. The amount of Ia present was estimated to be 50 per cent from the ratio of the extinction coefficients of Ia and II, and the shift in equilibrium composition of the mixture was in the direction consistent with this more polar solvent acting to stabilize the conformer which has the higher electrostatic energy, Ie.

The carbonyl bands in the infrared spectra of I in *cyclo*hexane and *n*-heptane showed two maxima of equal intensity which as before were not completely resolvable. From the non-polar character of these hydrocarbon solvents, one would expect the equilibrium mixture to be similar to that obtained for benzene. A reason for the apparent anomaly was evident when the molecular weight of I was determined in *cyclo*hexane solution at the concentration employed for the infrared study. The experimental value was 2·7 times greater than the value for the monomeric I, and a slight decrease of this association was observed when the determination was repeated with a more dilute solution. The infrared band attributed to Ie likewise decreased in intensity relative to the Ia band upon dilution. *Cyclo*hexanone (II) was also associated at the concentrations employed for the infrared study, and this compound afforded a significantly lower value for the experimentally determined molecular weight in a more dilute solution. Such association phenomena under similar circumstances are well known; for example, acetic anhydride is complexed in *cyclo*hexane.[13] The low melting point of *n*-heptane prevented molecular weight determinations from being conveniently performed with it as solvent, but the similarity of *n*-heptane and *cyclo*hexane and the virtually identical contour of the infrared carbonyl absorption curves of I obtained in the two solvents strongly suggest that I is also associated in *n*-heptane solutions. The amounts of Ia estimated from the infrared spectra would be lower than the values expected from the dielectric constants of these hydrocarbon solvents, for the association phenomena would be expected to create areas of high dielectric constant in the immediate vicinity of the carbonyl groups and, as a result, the equilibrium Ia $\rightleftarrows$ Ie would be displaced to the right.* No such effect was noticed in the

* *A priori* a reasonable alternative would be that one band was due to the associated form and the other to the unassociated form. This possibility was excluded on the basis that neither *cis*- nor *trans*-2-bromo-4-*t*-butyl*cyclo*hexanone (unpublished results), compounds which are constrained to essentially one conformation [14,15] but presumably still capable of carbonyl association, exhibits an analogous change in their respective carbonyl absorptions with change of solvent from carbon tetrachloride to *n*-heptane.

[12] R. N. Jones, W. F. Forbes and W. A. Mueller *Canad. J. Chem.* **35**, 504 (1957).
[13] D. C. Jones *J. Chem. Soc.* 1193 (1928).
[14] S. Winstein and N. J. Holness *J. Amer. Chem. Soc.* **77**, 5562 (1955).
[15] E. L. Eliel and R. S. Ro *Chem. & Ind. (Rev.)* 251 (1956).

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dipole moment study of I in heptane solution, presumably because these measurements were performed at lower (typical) concentrations where the association would be negligible. The ultraviolet absorption of I in *n*-heptane solution (see later) was obtained with a more dilute solution than was necessary for the infrared study and no association of I at this concentration (10^{-3} M) was evident.

The experimentally determined molecular weight of I in benzene at the concentration employed for the infrared study was identical with the calculated value. Since the absorption curves of I in carbon tetrachloride, chloroform, carbon disulfide, benzene and dioxane formed a progressive series, no association of I in these media was indicated. Freezing point determinations of I and II in dimethyl sulfoxide also established that no association occurred in this solvent, the experimental and the actual molecular weights being identical. Consequently the shift in the equilibrium in this case was attributed to the high dielectric character of the dimethyl sulfoxide medium. The infrared absorption of pure I (no solvent) had two bands of nearly equal intensity and the contour of the curve was similar to, though more completely resolved than, that afforded by I in *cyclo*hexane, *n*-heptane, and dimethyl sulfoxide. The estimated 50 per cent Ia composition, here again, is probably the result of association. This conclusion is supported by the fact that a simple ketone, acetone, is significantly dimerized even in the vapor phase.[16]

Table 2 records the estimated amounts of Ia present in the particular solvents employed for the infrared and the dipole moment studies. It is seen that the infrared analyses of the benzene and dioxane solutions of I, although of approximate nature in view of the difficulties, afforded values in reasonable agreement with those now calculated from the dipole moment data.

The ultraviolet absorption curves of I and II in carbon tetrachloride, *n*-heptane and 95 per cent ethanol were examined and the individual absorption maxima and intensities are summarized in Table 3. For each solvent I had its absorption maximum at longer wave length than the parent compound, the displacement of ca. 22 mμ indicating the presence of the *axial* conformer.[17] This does not contradict the infrared studies for the ultraviolet extinction coefficient of an equatorial α-bromoketosteroid in all solvents is appreciably lower than that of an axial α-bromoketosteroid, and, indeed, approximates that of the parent ketone at all wave lengths.[17] The amounts of Ie estimated to be present from the dipole moment and infrared studies are thus too small to be detected by a separate maximum in the ultraviolet spectra, but the maxima do show a skewing which is not inconsistent with the presence of comparable amounts of Ie and Ia in 95 per cent ethanol and somewhat less Ie in the other solvents. The difference between the intensity of the absorption maximum of an *axial* α-bromoketosteroid and the parent compound has been found to be at least 0·5 log ϵ units for ethanol solutions.[5] In the present study the difference in log ϵ of I and II was of this magnitude for the non-polar solvents but was appreciably lower for the 95 per cent ethanol medium (Table 3). This smaller difference in absorption intensity between I and II in the more polar solvent is consistent with a shift of the position of the equilibrium toward Ie as a consequence of the relatively high dielectric character of 95 per cent ethanol.

It would seem that the conclusions drawn by each previous investigator differ

[16] R. E. Pennington and K. A. Kobe *J. Amer. Chem. Soc.* **79**, 300 (1957).
[17] S. Mizushima *Structure of Molecules and Internal Rotation* p. 34. Academic Press, New York (1954).

primarily in degree because if the experimental data only are considered the qualitative conclusions from each study are in fact in agreement: (1) The infrared spectrum of I established the presence of both the *equatorial*- and the *axial*-2- bromo*cyclo*hexanone in carbon tetrachloride solution and (2) the dipole moment study can be most simply interpreted as the result of an equilibrium mixture of Ia and Ie the composition of which was affected by solvent. The spectral studies herein reported are hence consistent with all of the experimental data of the earlier work. The proposed modifications to describe the geometry of I and to account for the effect of the

TABLE 3.—ULTRAVIOLET ABSORPTION DATA FOR I AND II IN VARIOUS SOLVENTS

Solvent	λ_{max} mμ		log ε		(I–II)	
	I	II	I	II	λ_{max}	log ε
Carbon tetrachloride	312	290	2·02	1·41	+22	0·61
n-Heptane	312	291	1·98	1·18	+21	0·80
95 per cent ethanol	307	282	1·37	1·15	+25	0·22

solvent upon the electrostatic energies of the two conformers have served to effect a more complete correlation of the dipole moment studies and the calculated theoretical energy difference between the two conformers. An equilibrium ratio of *equatorial*- to *axial*-2-bromo*cyclo*hexanone which varies with solvent from 0·3 to 1·0 appears to be entirely consistent with all the data.

Consideration of a third conformer, the "flexible form",[18] would seem unnecessary for all the data may now be satisfactorily interpreted employing the simpler situation of the two conformers which are securely identified from other systems. Although a strict proof of the non-existence of the flexible form in the present system has not been obtained it would seem improbable that the flexible form would fit the observed facts, especially the spectral data.

Various alkylated 2-bromo*cyclo*hexanones have been studied by Corey and coworkers.[19] Their data also appear to be consistent with the conclusions drawn in the present work. It is of interest that these investigators concluded that 2-bromo-6,6-dimethyl*cyclo*hexanone existed as an equilibrium mixture of *axial* and *equatorial* conformers on the basis that two distinct carbonyl infrared absorption maxima were observed[19a] and the separation of 23 cm^{-1} for these bands apparently allowed easy resolution. In the present study the two infrared maxima of the homogeneous sample of I were 17 cm^{-1} apart while in various solvents the separation of the bands was only 12–15 cm^{-1} (Table 2). Fig. 2 shows that the resolution of the two maxima, although incomplete in the latter cases, was better for the homogeneous sample.

EXPERIMENTAL

2-*Bromo*cyclo*hexanone* (I). The procedure used was a modification of that described for the preparation of 2-chloro*cyclo*hexanone.[20] *Cyclo*hexanone, 10 g, and 30

[18] C. G. LeFevre and R. S. W. LeFevre *J. Chem. Soc.* 3549 (1956); W. Kwestroo, F. A. Meijer and E. Havinga *Rec. Trav. Chim. Pays. Bas.* **73,** 717 (1954).

[19] (a) E. J. Corey, T. H. Copie and W. A. Wozniak *J. Amer. Chem. Soc.* **77,** 5415 (1955); (b) E. J. Corey *Ibid.* **75,** 3297 (1953); (c) E. J. Corey *Ibid.* **76,** 175 (1954).

ml of water were placed in a three-necked flask equipped with a stirrer and a dropping funnel. Bromine, 16 g, was added dropwise to the stirred heterogeneous mixture during 1 hour, and a water-ice bath (5°) was employed to cool the reaction. When addition was completed, stirring was continued until the reaction mixture was colorless (30–60 min), the cooling bath being allowed to warm during this period. The crude product was isolated[20] and was distilled through a 2 ft column of the Podbielniak type to give 12 g (65 per cent) of I, b.p. 83° (6 mm), n_D^{20} 1·5096; reported[1] n_D^{27} 1·5093. Pure I could be stored protected from light at 0° for at least several weeks. *cyclo*Hexane and benzene solutions of I showed no evidence of decomposition (pink color) until after several days standing exposed to light at room temperature. Dimethyl sulfoxide solutions of I evidenced decomposition after 5–10 hr at room temperature.

Infrared studies. The spectra were obtained employing a Baird Double Beam Infrared spectrophotometer, AB Model. The concentrations of I and II in all solvents were as like as possible (ca. 0·12 M). The stability of pure I (no solvent) to infrared light was established when 3 identical and superimposable spectra were recorded for the sample at 5 min intervals, the cell with the sample being retained in the beam's path during the interim periods. For this reason and the fact that decomposition of various solutions of I was slow at room temperature, the spectra of I in solution are considered to be uncomplicated with impurities. Samples of I were subjected to simple vacuum distillation just before use. Commercial *cyclo*hexanone (II) was purified by distillation, n_D^{25} 1·4475; reported[21] n_D^{15} 1·4520.

n-Heptane and spectral-grade *cyclo*hexane were chromatographed on silica gel and the eluates were distilled from phosphorous pentoxide. Dioxane was purified in the usual way.[22] Thiophene-free benzene was dried by azeotropic distillation. The solvents carbon disulfide, chloroform, carbon tetrachloride were those designated "spectral-grade". Dimethyl sulfoxide, commercial grade, was purified by distillation, b.p. 76° (16 mm), m.p. 18·0–18·4°.

The amount of Ia in each solvent was calculated from the ratio of the optical density of Ia to the optical density of II at the same concentration and Beer's Law was assumed to hold for these calculations over the limited range necessary. The optical densities are recorded in Table 2.

Ultraviolet studies. The solvents carbon tetrachloride and *n*-heptane were those cited above and the spectra were recorded employing a Beckman Spectrophotometer with Spectracord attachment. The concentrations of I were $2{\cdot}55 \times 10^{-3}$ M in *n*-heptane, $2{\cdot}35 \times 10^{-3}$ M in carbon tetrachloride, $2{\cdot}70 \times 10^{-3}$ M in 95 per cent ethanol; and the corresponding concentrations of II were $3{\cdot}03 \times 10^{-2}$ M, $2{\cdot}78 \times 10^{-3}$ M, and $2{\cdot}40 \times 10^{-2}$ M.

Melting point determinations. The *cyclo*hexane used for the spectral studies was not of sufficient purity for ordinary freezing point determinations. The impurities present formed solid solutions, a continuous lowering of temperature being observed with determination of the freezing point of the solvent itself. Accordingly, a modified Rast method was employed. The solution, placed in a simple freezing point apparatus, was cooled to afford crystallization. The bath temperature was allowed to rise and the

[20] M. S. Newman, M. D. Earbman and H. Hipsher *Organic Synthesis Coll.* Vol. III, p. 188. John Wiley, New York (1955).
[21] E. H. Huntress and S. P. Mulliken *Identification of Pure Organic Compounds* p. 382. John Wiley, New York (1946).
[22] L. Fieser *Experiments in Organic Chemistry* p. 369. D. C. Heath and Co. New York (1941).

temperature of the solution was recorded as a function of time. The plot of the data afforded a smooth curve and the point of intersection of the line drawn through the first portion of the curve (melting of the solid suspended in the solution) with the line drawn through the second portion of the curve (warming of the clear solution) was taken as the melting point. Two or three determinations were performed for each solution and excellent reproducibility of the melting points was obtained. That I did not decompose during the experiments was concluded from the fact that pure I could be recovered quantitatively from these solutions. The data are recorded in Table 4.

TABLE 4

Compound	Molal concentration[b]	Observed depression	Molecular weight exp./calcd. value
	Solvent—*cyclo*hexane, $K_f = 20.3°$[a]		
I	0·155	1·1790°	2·7
I	0·016	0·1315°	2·4
II	0·154	0·6563°	4·8
II	0·017	0·1313°	2·6
n-heptane	0·153	3·034°	1·02
	Solvent—benzene, $K_f = 5·12°$		
I	0·154	0·798°	1·0
	Solvent—dimethyl sulfoxide, $K_f = 2·04°$[c]		
benzene	0·113	0·232°	1·00
II	0·111	0·222°	1·03
	Solvent—dimethyl sulfoxide, $K_f = 4·12°$[c]		
benzene	0·114	0·469°	1·00
I	0·114	0·464°	1·01

[a] Calculated from the heat of fusion, R. A. Ruehrwein and H. M. Huffman *J. Amer. Chem. Soc.* **65**, 1620 (1943).

[b] Molal concentrations here correspond closely to (molar) concentrations employed for infrared studies.

[c] Two different samples of solvent were employed and the melting point depression was determined using benzene as the standard compound.

Molecular geometry. II was placed in the co-ordinate system as used for "*cyclo*hexylidine", and the co-ordinates of the ring carbons and hydrogens of II were assigned the values obtained earlier for the hydrocarbon.[4] The co-ordinates of the carbon having the exocyclic substituent were −0·732, 0, +0·258, and thus a line drawn from the origin to the carbonyl carbon of II described an angle with the *xy*-plane of 19°25′ and was 0·778 Å in length. Since the carbonyl carbon–oxygen bond (length 1·22 Å) is simply an extension of this line, the oxygen atom was 1·998 Å from the origin and had co-ordinates relative to the attached carbon of −1·151, 0, +0·406.

This model of II was used to calculate the dipolar angles involving the carbonyl group and the axial and equatorial 2-substituents. The method is indicated for the equatorial substituent. The co-ordinates of the equatorial hydrogen were −0·538, +0·808 and +0·481[4] relative to the attached carbon. Thus a triangle may be constructed, the three corners of which are the origin and the co-ordinates given above for the oxygen and hydrogen. The oxygen-hydrogen distance in the triangle was thus 1·017 Å and knowing the three sides of the triangle, the desired angle between C=O

and (e) C—H was calculated to be 51°54′. The axial hydrogen, in a similar manner, afforded a dipole angle of 109°51″.

Calculation of electrostatic energy of Ia *and* Ie. The modified equation (2) was employed for heptane solution:

$$E_e = \frac{\mu_{C-Br}\mu_{C=O}}{2r^3}(\cos\chi - 3\cos\alpha_1\cos\alpha_2) \tag{2}$$

The quantities

$$r = [a^2\sin^2\theta_1 + b_2\sin^2\theta_2 - 2ab\sin\theta_1\sin\theta_2\cos\phi + (c_0 - a\cos\theta_1 - b\cos\theta_2)^2]^{\frac{1}{2}},$$

$$\cos\alpha_1 = (a^2 + r^2 - c_0^2 - b^2 + 2c_0 b\cos\theta_2)/2ar,$$

$$\cos\alpha_2 = (b^2 + r^2 - c_0^2 - a^2 + 2c_0 a\cos\theta_1)/2br,$$

$$\cos\chi = \sin\theta_1\sin\theta_1\cos\phi - \cos\theta_1\cos\theta_2$$

are those described.[23] In particular, the dipole angles χ obtained by the vector analyses of Ia and Ie afford the dihedral angles (ϕ) 16°17′ for Ie and 102°13′ for Ia. The bond lengths a = C=O = 1·22 Å, b = C—Br = 1·91 Å, c_0 = C—C = 1·54 Å, and the bond angles θ_1 = C—C=O = 120°, θ_2 = C—C—Br = 109°28′ were employed and the individual bond moments were assigned as μ_{C-Br} = 1·91 D, μC=O = 2·83D. The electrostatic energies of Ia and Ie were found to be −1·71 and +0·22 kcal/mole, respectively.

Acknowledgements—We are indebted to Prof. R. Kikuchi for helpful discussion with regard to the theoretical calculations and to Dolores J. Phillips for the infrared and ultraviolet absorption spectra.

[23] C. P. Smyth, R. W. Dornte and E. B. Wilson, Jr. *J. Amer. Chem. Soc.* **53**, 4242 (1931).

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A TWO-STEP SYNTHESIS OF ALLENES FROM OLEFINS

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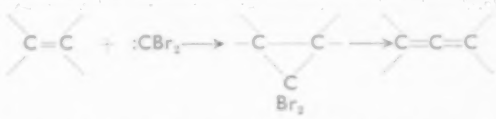
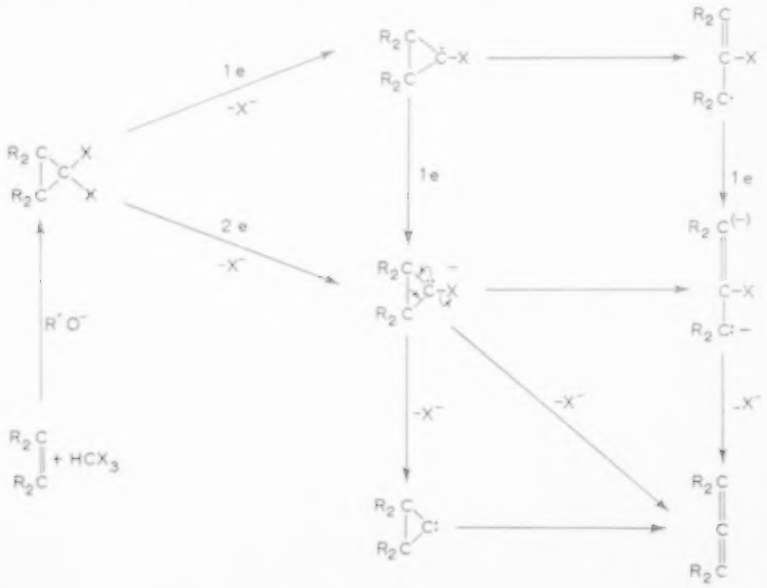
(*Received* 28 *June* 1957)

Abstract—In a two-step sequence, of which the first step involves addition of dibromocarbene to an olefin and the second involves reaction of the resulting substituted 1,1-dibromo*cyclo*propane with magnesium or sodium, allenes are obtained. The overall structural change involves the insertion of



a single carbon atom between the two of the original double bond and therefore represents a novel way of increasing carbon chain lengths by one atom.

1,1-DIHALO*cyclo*PROPANES are conveniently available in one step through the recently discovered reaction of Doering and Hoffmann in which an olefin is treated with haloform and alkoxide ion.[1,2] Theoretical examination of the mechanistic possibilities leads to the prediction that reduction of these 1,1-dihalo*cyclo*propanes by active metals may produce allenes. As depicted below, the accepting of two electrons, either in two steps or one, may lead to elimination of both halogen atoms as halide ion and cleavage of the *cyclo*propane ring to an allene.



[1] W. von E. Doering and A. K. Hoffmann *J. Amer. Chem. Soc.* **76**, 6162 (1954).
[2] Several examples giving additional support to the generality of the reaction have been carried out by P. S. Skell and O. Y. Garner *J. Amer. Chem. Soc.* **78**, 5430 (1956).

The chance of realizing the hypothetical reaction with the *dichloro* derivatives seems remote on the basis of the work of Gustavson[3] who has found 1,1-dichloro-*cyclo*propane to be stable to sodium metal at 140°. Consistently, 1,1-dichloro-2,2,3-trimethyl*cyclo*propane liberates no chloride ion on treatment with sodium metal at 180°, alone, in *bis*-(2-ethoxyethyl)ether and on alumina in the high surface form. Neither does lithium nor magnesium under a variety of conditions remove any halogen.

With dibromo*cyclo*propane derivatives, however, it is possible to realize the reaction. Both magnesium and sodium are capable of converting substituted dibromo-*cyclo*propanes to allenes in varying yield. Thus, with magnesium in ether *cis*-1,1-dibromo-2,3-dimethyl*cyclo*propane (from *cis*-butene and bromoform[4]) is converted to 2,3-pentadiene in low yield (16 per cent of theory). The identification follows from the presence in the i.r. of the 5·06 μ band characteristic of allenes[5] and the coincidence of physical properties with those reported.[6] By vapor phase chromatographic (v.p.c.) analysis this sample was found to be contaminated with 3 per cent of 2-pentyne. Reaction of 1,1-dibromo-2-*n*-propyl*cyclo*propane with magnesium in ether yields 1,2-hexadiene (62 per cent of theory), identified by i.r. (5·09 μ), comparison of physical properties with those reported[7] and oxidation to butyric acid. From 1,1-dibromo-2,2,3-trimethyl*cyclo*propane in tetrahydrofuran, magnesium gives 2-methyl-2,3-pentadiene.

In our hands sodium reacts best in the form of its high surface dispersion on alumina. Under reduced pressure without solvent, 1,1-dibromo-2-*n*-propyl*cyclo*-propane is converted in excellent yield (96 per cent of theory) to a mixture of C_6H_{10} hydrocarbons. Separation by v.p.c. gives three components, the major one (64 per cent) being 1,2-hexadiene and the two minor ones apparently being acetylenes. The more reactive metal has thus effected the allene-acetylene interconversion, a reaction well recognized as the result of the action of strong bases.[5a] No extensive effort has been made to define the conditions necessary to minimize the isomerization.

No choice between the modes of cleavage formulated above can be made with assurance. The first scheme depicts the opening of an intermediate *cyclo*propyl radical to the corresponding allyl radical. Although this kind of change occurs at higher temperature, it does not occur in the low-temperature photochemical chlorination of *cyclo*propane[8] to *cyclo*propyl chloride. Accordingly, the radical scheme does not seem particularly attractive. The second scheme, involving cleavage of the *cyclo*propyl carbanion to the allyl carbanion, also seems unlikely, in view of the failure of *cyclo*propyl carbanion itself to isomerize.[9,10] It becomes far more attractive if ring opening and loss of halide ion be assumed to occur *simultaneously*.

The carbene mechanism will be tested partially by examining the irradiation of diazo*cyclo*propane. The necessary condition that 1,1-dihalides and active metals

[3] G. Gustavson *J. Prakt. Chem.* [2] **42**, 496 (1890); [2] **43**, 396 (1891).
[4] W. von E. Doering and P. M. LaFlamme *J. Amer. Chem. Soc.* **78**, 5447 (1956).
[5a] T. L. Jacobs, R. Akawie and R. G. Cooper *J. Amer. Chem. Soc.* **72**, 1272 (1950).
[5b] J. H. Wotiz *J. Amer. Chem. Soc.* **73**, 692, 5503 (1951); **74**, 1860 (1952); *J. Organ. Chem.* **22**, 207 (1957).
[6] American Petroleum Institute Research Project 44 *Selected Values of Properties of Hydrocarbons and Related Compounds* Table 11a (Part I) Carnegie Institute of Technology, Department of Chemistry, Pittsburgh, Penn. (1952).
[7] G. F. Hennion and J. J. Sheehan *J. Amer. Chem. Soc.* **71**, 1964 (1949).
[8] J. D. Roberts and P. W. Dirstine *J. Amer. Chem. Soc.* **67**, 1281 (1945).
[9] J. D. Roberts and V. C. Chambers *J. Amer. Chem. Soc.* **73**, 3176 (1951).
[10] V. A. Slabey *J. Amer. Chem. Soc.* **74**, 4928 (1952).

should give carbenes appears to be fulfilled. In unpublished work, methylene iodide and finely divided zinc-copper couple react with *cis*- and *trans*-butene to give *cis*-1,2-dimethyl*cyclo*propane, *cis*-pentene and 2-methyl-2-butene and *trans*-1,2-dimethyl-*cyclo*propane, *trans*-pentene and 2-methyl-2-butene respectively. These reactions are comparable to that of diazomethane with *cis*- and *trans*-butene.[4]

To the previously known conversions of the double bond through the 1,1-dibromo-*cyclo*propane group to a methyl ethane group[1] and to a *cyclo*propane ring,[1,4] this reaction adds the conversion to an allene in only two steps by the insertion of a single carbon atom between the two of the original olefin. These transformations of the 1,1-dibromo*cyclo*propanes are potentially useful in synthesis and are summarized below:

Examination of the behavior of some bicyclic dibromo*cyclo*propanes obtained from bromoform and cyclic olefins is in progress and will be reported later. This investigation has been supported since its inception in the fall of 1954 by a much appreciated grant from the Research Corporation, New York City.

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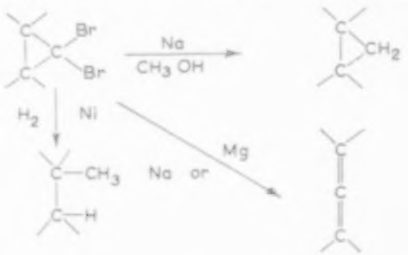
EXPERIMENTAL*

Preparation of allenes from 1,1-*dibromo*cyclo*propanes*

(1) *With magnesium*

(a) 2,3-*Pentadiene from* cis-1,1-*dibromo*-2,3-*dimethyl*cyclo*propane*. *cis*-Dibromo-2,3-dimethyl*cyclo*propane (45·6 g, 0·20 mole) in 100 ml of anhydrous ether was added dropwise to a stirred mixture of 24·3 g (1·00 g atom) of magnesium and 200 ml of ether in a 500-ml, 3-necked flask equipped with mechanical stirrer, dry-ice condenser and Ascarite drying tube. The reaction started easily on warming and was essentially complete after 2 hr under gentle reflux. A magnesium bromide-ether phase separated



midway through the addition. The reaction mixture was carefully hydrolyzed with ice-water. The ether phase was separated and later united with three 25 ml portions of ether used to extract the aqueous phase. Following addition of a trace of hydroquinone, the dried (magnesium sulfate) ether solution was fractionated through a 10 in. helix-packed column giving (1) b.p. 40–46°; 1·80 g; (2) b.p. 46·0–48·0°; 0·60 g and (3) b.p. 48–49·0°; 1·60 g. The infra-red spectrum of (3) showed a very strong

* Boiling points are uncorrected. Infra-red spectra were taken with a Perkin-Elmer Model 21 infra-red spectrophotometer with sodium chloride optics, samples neat of 0·1 and 0·025 mm thickness. V.p.c. (vapor phase chromatographic) analyses were made with a Perkin-Elmer Model 154 instrument, using a 2 m "A" column. Elementary analyses were performed by Schwarzkopf Microanalytical Laboratory, 56–19 37th Avenue, Woodside 77, New York.

peak at 5·06 μ. Redistillation afforded 2,3-pentadiene; b.p. 48–48·5°/771 mm; n_D^{25} 1·4202, d_4^{25} 0·7020 (reported[8] b.p. 48·27°/760 mm, n_D^{25} 1·4251); MR_D: found: 24·38; calcd: 23·30[11] (Found: C, 88·0; H, 12·0. C_5H_8 requires C, 88·2; H, 11·8 per cent).

Examination of the crude material by means of v.p.c. at 10 lb of He and 25° indicated 96·9 per cent, 2,3-pentadiene and 3·1 per cent of 2-pentyne, having an infra-red spectrum identical to that of an authentic sample obtained from the Farchan Research Laboratories, Cleveland, Ohio. Bromine in carbon tetrachloride was standardized against pure 2-methyl-2-butene. The allene (112·85 mg) in a sealed ampoule was crushed under carbon tetrachloride and titrated against a blank. The sample absorbed 5·250 ml of 0·282 + 0·011 M bromine solution, or 0·89 mole of bromine per mole of hydrocarbon. This result agrees with that of Acree and La Forge[12] who found that the same compound under similar conditions absorbed 0·85 mole of bromine.

(b) 1,2-*hexadiene from* 1,1-*dibromo*-2-n-*propyl*cyclo*propane*. From 1-pentene, bromoform and potassium *t*-butylate, 1,1-dibromo-2-*n*-propyl*cyclo*propane (b.p. 72°/12 mm; n_D^{25} 1·5023) was prepared in 55 per cent of the theoretical yield through the kindness of Mr. Wm. A. Henderson, Jr. of this laboratory. A solution of 24·2 g (0·10 mole) of this dibromide in 25 ml of ether was added slowly to 2.67 g (0·11 atom) of magnesium in 25 ml of ether. The reaction was worked up as before giving 2·65 g (45 per cent) of material, b.p. 74–75°, and 11·23 g of recovered starting material. The yield based on unrecovered starting material was 62 per cent of theory. Analysis by v.p.c. of the crude material indicated it to be 92 per cent 1,2-*hexadiene*. A pure sample obtained by v.p.c. possessed a very strong peak in the infra-red at 5·09 μ; b.p. 75°; n_D^{20} 1·4276 (unreported[7] b.p. 74·6–74·8°; n_D^{25} 1·4282) (Found: C, 87·6; H, 12·0. C_6H_{10} requires C, 87·7; H, 12·3). Using the procedure of Hennion and Sheehan[7] 0·25 g of the diene was oxidized with alkaline permanganate to an acid from which a *p*-bromophenacyl ester was prepared, m.p. 61–62°; mixed m.p. with an authentic sample of *p-bromophenacyl*-butyrate was 62–63°.

(c) 2-*Methyl*-2,3-*pentadiene from* 1,1-*dibromo*-2,2,3-*trimethyl*cyclo*propane*. From powdered potassium *t*-butylate (1 mole), bromoform (1 mole) and 300 g of 2-methyl-2-butene, 1,1-dibromo-2,2,3-trimethyl*cyclo*propane (b.p. 63–66°/15 mm) was prepared in 53 per cent yield by the usual reaction. A solution of 24·2 g (0·1 mole) of this dibromide in 50 ml of tetrahydrofuran (dried by distillation from Grignard) was treated with 4·86 g (0·2 g atom) of magnesium in dry tetrahydrofuran. Hydrolysis with water caused separation of a hydrocarbon phase which was washed repeatedly with water and dried over magnesium sulfate. Distillation gave 1·72 g of starting material and 2·75 g (34 per cent) of 2-*methyl*-2,3-*pentadiene*; b.p. 72·5° (reported[13] b.p. 71·5–72·5°); n_D^{25} 1·4350; showing a weak peak at 5·09 μ. (Found: C, 87·9; N, 12·0. C_6H_{10} requires C, 87·7; H, 12·3 per cent). The qualitative test for allenes described by Bouis[14] in which the allene is added to an ethanolic mercuric chloride solution was positive, a copious white precipitate being formed.

[11] Using the value 0·44 for the system C—C—C given by T. L. Jacobs and W. F. Brill *J. Amer. Chem. Soc.* **75**, 1316 (1953).
[12] F. Acree and F. B. La Forge *J. Organ. Chem.* **5**, 430 (1940).
[13] S. Lebedew and B. Mereschkowski *J. Russ. Phys. Chem. Soc.* **45**, 1249 (1913); *Chem. Zentr.* **1**, 1409 (1914); *Chem. Abstr.* **8**, 3204 (1914).
[14] M. Bouis *C. R. Acad. Sci., Paris* **182**, 788 (1925).

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(II) *With sodium*

(b) 1,2-*Hexadiene from* 1,1-*dibromo*-2-n-*propyl*cyclopropane. High-surface sodium on alumina was prepared as follows. Chromatographic alumina (80–200 mesh, 103 g) was dried at 500° for 15 hr, cooled and placed in a 3-necked, 500 ml flask where it was further dried at 200° for 2 hr at 1 mm with stirring. The flask was cooled to 150° and, under nitrogen, 14·0 g (0·61 g atom) of sodium was added. Stirring was continued until a dark gray dispersion formed. An additional funnel and an exit tube connected to a trap at −78° were attached. At 5 mm, 24·2 g (0·1 mole) of 1,1-dibromo-2-*n*-propyl*cyclo*propane was added dropwise with stirring at room temperature. The reaction was moderated by intermittent cooling to avoid the distillation of starting material. After the addition had been completed, pumping and stirring were continued one more hour. The crude product (7·64 g, 95·6 per cent) was examined by v.p.c. and appeared to be a mixture of 1,2-*hexadiene* (63·5 per cent) and two other components (26·5 and 10·0 per cent respectively) which had infrared peaks at 4·5 μ and were probably 1-hexyne and 2-hexyne.

(b) 2,3-*Pentadiene from* trans-1,1-*dibromo*-2,3-*dimethyl*cyclo*propane*. A suspension of 14·0 g (0·61 g atom) of sodium on 70 g of alumina was prepared as above. Into the same apparatus, 100 ml of *cis*-decalin (dried by distillation from sodium-on-alumina) was put. Thereupon, a solution of 57·0 g (0·25 mole) of *trans*-1,1-dibromo-2,3-dimethyl*cyclo*propane in 50 ml of *cis*-decalin was added dropwise with stirring over a period of 2·5 hr at 25 mm and room temperature. The exothermic reaction was cooled intermittently to maintain the contents at 35°. After an additional hour, the trap had collected 17·6 g of liquid, from which 7·46 g (44 per cent) of nearly pure 2,3-*pentadiene* b.p. 48·0–48·5°, was obtained by distillation.

Tetrahedron, 1958, Vol. 2, pp. 80–87. Pergamon Press Ltd., London

THE SYNTHESIS OF AROMATIC A RING 9//10-SECOSTEROIDS FROM UNSATURATED 3,11-DIKETO STEROIDS

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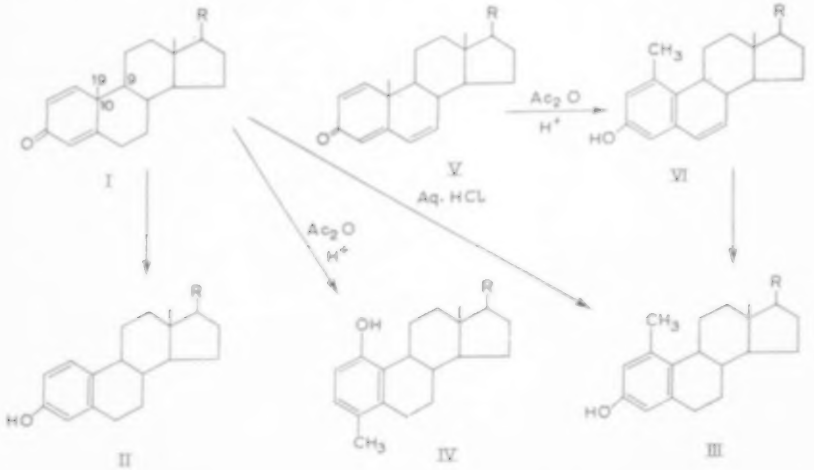
(*Received* 23 *July* 1957)

Abstract—The preparation of aromatic A ring 9//10 secosteroids via the pyrolysis of unsaturated 3,11-diketosteroids is described.

THE partial synthesis of aromatic A ring steroids is based on the pioneering work of Inhoffen who showed that 3-keto-1,4-dienes could be converted to aromatic A ring steroids by two methods. In the first method the 3-keto-1,4-diene (I) was pyrolyzed in a sealed tube to give a low yield of the phenol (II).[1] Significantly higher yields were



reported for this reaction when the steroid, dissolved in a hydrogen-donating solvent such as mineral oil, was passed through a heated tube.[2] Recently this aromatization reaction was utilized for the preparation of aromatic A ring steroids containing a

[1] H. H. Inhoffen *Angew. Chem.* **53,** 471 (1940).
[2] H. H. Inhoffen *Ibid.* **59,** 207 (1947); C. R. Addinall Fiat Final Report 996 *The Commercial Development and Manufacture of Synthetic Hormones in Germany.* Office of the Publication Board, U.S. Dept. of Commerce; E. B. Hershberg, M. Rubin and E. Schwenk *J. Org. Chem.* **15,** 292 (1950).

variety of functional groups.[3] Yields up to 40 per cent were reported in certain cases. This reaction was also successfully employed in the presence of an 11α- or 11β-hydroxyl group and 9(11)-unsaturation.[4]

The second general method involved the dienone-phenol rearrangement of the 3-keto-1,4-diene in a non-aqueous acid system.[2,5] Originally the product of this rearrangement was thought to be the 1-methyl steroid (III), however, later work established (IV) as the correct structure.[6–9] Dienone-phenol rearrangement of a 3-keto-1,4,6-triene (V) afforded a true 1-methyl steroid (VI). Subsequent hydrogenation of the double bond at 6 formed the phenol (III).[7]

Recently the aromatization of 3-keto-1,4-dienes in the presence of aqueous mineral acid was reported to form chiefly the 1-methyl phenols (III) as well as lesser amounts of the 1-hydroxy-4-methyl phenols (IV).[10]

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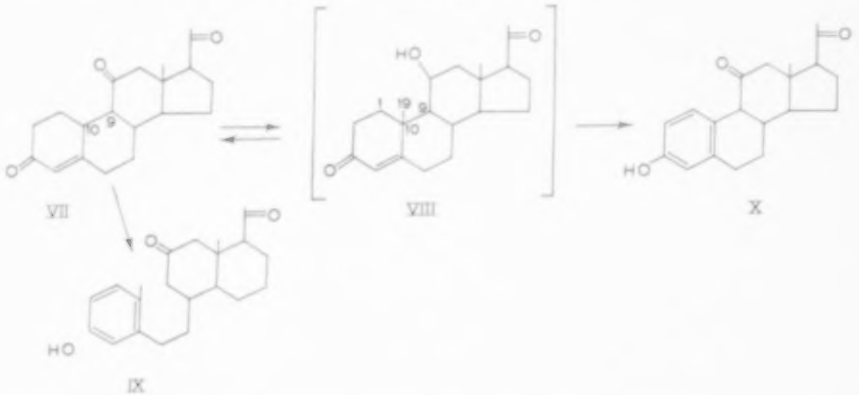
The formation of the phenol (II) by pyrolysis of a 3-keto-1,4-diene may be interpreted according to the Staudinger-Schmidt double bond rule which states that pyrolytic fission of a C-C bond in unsaturated compounds is most likely to occur at an allylic position.[11] Thus in structure (I) the 10,19 and the 9,10-bond both have a 1,3 relationship to two points of unsaturation (Δ^1 and Δ^4). The likely points of fission are therefore at 10–19 and 9–10 with the exocyclic 10,19-bond being preferred.

In the light of this rule two products are probable from the pyrolysis of a 3,11-diketo-4-ene, such as 11-ketoprogesterone (VII).

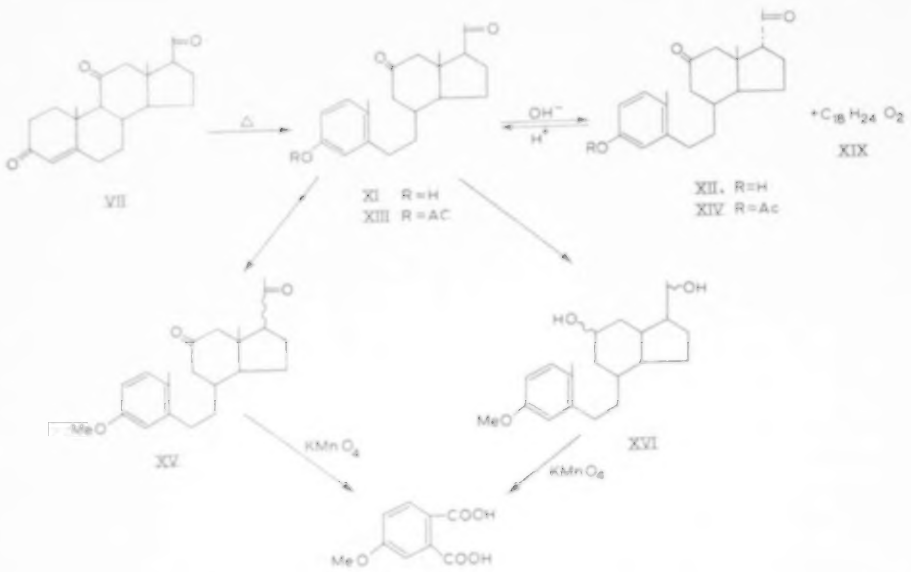


VII VIII X

IX

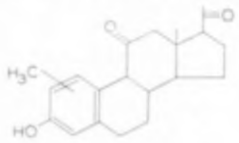
If the 11-keto group should exert its influence in the enol form (VIII), bonds 10,19 and 10,1 both would be 1,3 to two points of unsaturation and fission of the 10,19 bond again might be expected. If the effect of the 11-keto group is due to its keto form, only the 9,10-bond is 1,3 to two points of unsaturation and a 9//10 secosteroid (IX) is the likely product. The secosteroid (IX) was actually isolated, thus establishing a new type of aromatic A ring product obtainable from unsaturated 3-ketosteroids.

[3] *Inter alia* C. Djerassi, G. Rosenkranz, J. Iriarte, J. Berlin and J. Romo *J. Amer. Chem. Soc.* **73,** 1523 (1951); C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann and J. Pataki *Ibid.* **72,** 4534 (1950).
[4] B. J. Magerlein and J. A. Hogg *Ibid.* **79,** 1508 (1957).
[5] H. H. Inhoffen and G. Zühlsdorff *Ber. Dtsch. Chem. Ges.* **74,** 604 (1941).
[6] R. B. Woodward and T. Singh *J. Amer. Chem. Soc.* **72,** 494 (1950).
[7] C. Djerassi, G. Rosenkranz, J. Romo, J. Patakai and St. Kaufmann *Ibid.* **72,** 4540 (1950).
[8] R. B. Woodward, H. H. Inhoffen, H. O. Larson and K. Menzel *Ber. Dtsch. Chem. Ges.* **86,** 594 (1953).
[9] A. S. Dreiding and A. Voltman *J. Amer. Chem. Soc.* **76,** 537 (1954).
[10] A. S. Dreiding, W. J. Pummer and A. J. Tomasewski *Ibid.* **75,** 3159, 3162 (1953).
[11] R. C. Fuson *Advanced Organic Chemistry* p. 15. John Wiley, New York (1950).



11-Ketoprogesterone was fused in an open vessel and heated to about 350°. A phenolic fraction, obtained in 65 per cent yield, chiefly consisted of three parts of (XI) and one part of (XII). When (XI) was treated with alkali, a mixture of (XI) and (XII) was obtained. A high yield of (XI) was obtained when (XII) was refluxed with aqueous acid. Compound (XII) is more dextrorotatory than is (XI)[(XII) $[\alpha]_D + 43°$ in acetone; (XI) $[\alpha]_D - 35°$ in acetone]. These facts suggest that (XI) and (XII) are isomeric at a carbon atom α to a carbonyl. Because of the rotational change C–17 was chosen as the point of isomerization and the 17 β configuration assigned to (XII).

Before assigning the seco structure to the pyrolysis products of 11-ketoprogesterone, the phenolic formulations (X) and (XVIII) were considered.



XVIII

Structure (X) is eliminated by an accurate determination of the molecular weight as 327·7 (calcd. for $C_{21}H_{28}O_3$, 328·4)* which clearly indicates that the methyl group is still present.

The physical data are insufficient to eliminate structure (XVIII). The major pyrolysis product (XI) was methylated forming the oily methyl ether (XV) which on

* The authors are indebted to Dr. J. Shell of the Upjohn Company for the crystallographic analysis. Dr. Shell reports that the extremely high negative birefringence exhibited by these crystals is in keeping with a 9//10 seco compound, that is, the molecule is less planar and more rod shaped than the usual steroid molecule. These data are accurate to ±1 per cent.

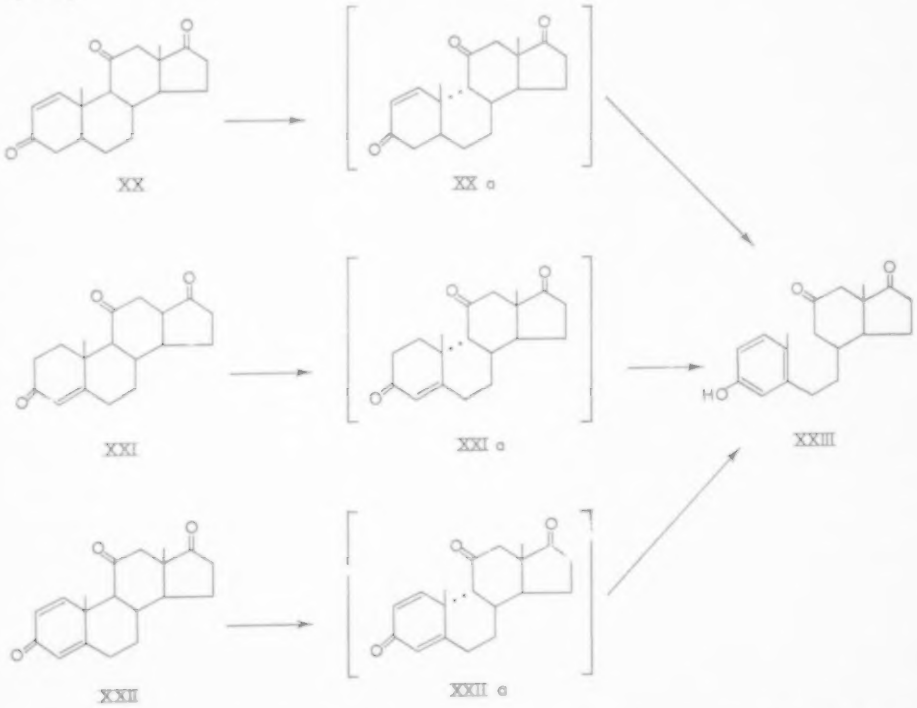
exhaustive oxidation yielded the known 4-methoxyphthalic acid. Since 4-methoxyphthalic acid could be formed only from a disubstituted phenol, structure (XVIII) is eliminated.

From these data we conclude that the seco structures (XI) and (XII) for the pyrolysis products of 11-ketoprogesterone are most consistent with the known facts.

A third crystalline product (XIX) was isolated in 0·4 per cent yield from this pyrolysis reaction. The elemental analysis for (XIX) is consistent with the empirical formula $C_{18}H_{24}O_2$. Infra-red data indicate phenolic hydroxyl and carbonyl.

The pyrolysis product of 4-androstene-3,11,20-trione (XXI) is assigned by analogy the seco structure (XXIII).

Having demonstrated that 9//10-secosteroids are formed in the pyrolysis of 3,11-diketo-4-enes our interest turned to 3,11-diketo steroids possessing unsaturation at 1 or at 1 and 4. In both of these cases the 9-10 bond is allylic to one more point of unsaturation than is the 10,19-bond. Therefore one might expect that the pyrolytic products from these would be formed after initial fission of the 9,10 bond. Pyrolysis of 1-androstene-3,11,17-trione (XX) or 1,4-androstadiene-3,11,17-trione (XXII) gave the same compound (XXIII) obtained by the pyrolysis of 4-androstene-3,11,17-trione (XXI).



An explanation for the formation of 9//10-secosteroids may be formulated by considering the mechanism of the aromatization reaction. Pyrolytic reactions are generally accepted to proceed by free radical mechanisms.[12] The pyrolysis of a 3-keto-1,4-diene therefore could first involve the loss of the 19-CH_3 radical leaving

[12] E. W. R. Steacie *Free Radical Mechanisms* p. 61. Reinhold Publishing Corporation, New York (1946).

the steroid radical which could then abstract a hydrogen atom from the solvent or from another steroid molecule to yield the phenol.

In the case of the Δ^1, Δ^4 or $\Delta^{1,4}$-3,11-diketo steroids, as previously noted, the 9,10-bond has one more 1,3 relationship to points of unsaturation than does the 10,19-bond. Therefore in the 11-keto series the presence of the 11-keto group causes the initial cleavage to occur at 9,10 to form the diradicals (XXa), (XXIa), (XXIIa), respectively. The diradicals (XXa), (XXIa), and (XXIIa) abstract the necessary hydrogen atoms to form the seco structure shown (XXIII).

EXPERIMENTAL*

3-*Hydroxy*-9//10-*seco*-1,3,5(10)-*pregnatriene*-11,20-*dione* (XI) *and* 3-*Hydroxy*-9//10-*seco*-17-iso-1,3,5(10)-*pregnatriene*-11,20-*dione* (XII)

Ten grams of 11-ketoprogesterone (I) was heated at 365–370° for 45 min, after which time gassing had noticeably decreased. About 165 ml (24 per cent of 1 mole) of gas was evolved in this reaction. Infrared analysis of this gas showed it to consist of methane, ethylene, carbon dioxide and carbon monoxide. The ratio of methane to ethylene was about 40 to 1. Benzene (25 ml) was added to the warm melt and then 100 ml of ether. The solution was separated into phenolic and neutral fractions with 5 per cent sodium hydroxide. The neutral fraction weighed 3·5 g. This dark tarry material was chromatographed over Florisil† but no definite fractions were obtained. Papergram analysis showed a small amount of 11-ketoprogesterone along with numerous unidentified materials. The phenolic fraction, 6·4 g, was dissolved in benzene and chromatographed over 500 g of Florisil. Elution with Skellysolve B‡ plus 12 per cent acetone yielded Fraction A of 2·99 g. Further elution with this solvent and also with Skellysolve B plus 20 per cent acetone gave 0·98 g of Fraction B.

Fraction A was recrystallized from 2-propanol (yield 2·13 g, 21·3 per cent). It melted 132–136°. Several recrystallizations from ethyl acetate gave an analytical sample of 3-hydroxy-9//10-seco-1,3,5(10)-pregnatriene-11,20-dione (XI) m.p. 138–139°; $[\alpha]_D + 43°$ (acetone); λ_{max}^{EtOH} 281 mμ, a_M 2,225; 287 mμ, a_M 1,975; ν_{max}^{Nujol} 3205, 1705, 1675, 1618, 1583, 1497 cm^{-1}.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76·79; H, 8·59; Mol. wt. 327·76. Found: C, 76·53, 76·63; H, 8·38, 8·25; Mol. wt. 328·4.§

Recrystallization of Fraction B from 2-propanol yielded 780 mg of 3-hydroxy-9//10-seco-17-*iso*-1,3,5(10)-pregnatriene-11,20-dione (XII), m.p. 153–157°. Recrystallization from ethyl acetate-Skellysolve B gave an analytical sample m.p. 159·5–160·5°; $[\alpha]_D - 35°$ (acetone); λ_{max}^{EtOH} 281 mμ, a_M 2,225; 287 mμ, a_M 1,975; ν_{max}^{Nujol} 3240, 1705, 1690, 1617, 1585, 1498 cm^{-1}.

Anal. Found: C, 77·19; H, 8·73.

From the forefractions of a similar pyrolysis a crystalline compound m.p. 178–179°, $[\alpha]_D + 15°$ (acetone); ν_{max}^{Nujol} 3230, 1687, 1675, 1618, 1585, 1502 cm^{-1} was isolated in 0·4 per cent yield.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79·37; H, 8·88. Found: C, 79·45, 79·18; H, 8·72, 8·76.

* Melting points are uncorrected.
† A synthetic magnesia—silica gel made by the Floridin Company, Warren, Pa.
‡ A saturated hydrocarbon fraction, b.p. 60–71°.
§ See footnote on p. 82.

Isomerization of compound (XII) *to compound* (XI)

A solution of 230 mg of (XII), m.p. 153–158°, in 6 ml of ethanol and 0·6 ml of concentrated hydrochloric acid was heated under reflux for 30 min. The solvent was evaporated under vacuum and the product crystallized from ethyl acetate-Skellysolve B to give 90 mg m.p. 129–132°. Recrystallization from the same solvent gave 50 mg m.p. 133–135·5°. This material showed no m.p. depression when admixed with (XI). Its infra-red curve was identical with that of (XI).

Conversion of 17 g of crude (XII) (chromatographic fraction) to (XI) as described gave about 60 per cent of material m.p. 134–138·5°.

Partial isomerization of compound (XI) *to compound* (XII)

(A) *By alkali.* A solution of 100 mg of (XI) free from (XII), as shown by papergram, in 5 ml of 5 per cent sodium hydroxide was heated to boiling and permitted to stand for 4 hr. Acidification of the solution gave an oil which by papergram consisted of 75 per cent (XI) and 25 per cent (XII).

(B) *By heat.* Fifty milligrams of (XI) free from (XII), as shown by papergram, was heated at 360° for 15 min. Papergram showed the resulting oil to be 64 per cent (XI) and 36 per cent (XII).

3-*Acetoxy*-9//10-*seco*-1,3,5(10)-*pregnatriene*-11,20-*dione* (XIII)

A solution of 200 mg of (XI) in 1·5 ml of acetic anhydride and 1·5 ml of pyridine was warmed on a steam bath for ninety minutes. The cooled reaction mixture was poured into water with vigorous stirring. The crude product obtained by filtration was dried and recrystallized from ethyl acetate-Skellysolve B to give 200 mg (87·5 per cent) of (XIII) m.p. 138–139°. Further crystallization yielded an analytical sample m.p. 139–140°, λ_{max}^{EtOH} 268 mμ, a_M 558; 274·5 mμ; a_M 548. ν_{max}^{Nujol} 1745, 1692, 1612, 1585, 1500, 1219 cm^{-1}.

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74·56; H, 8·16. Found: C, 74·53, 74·71; H, 8·31, 8·08.

3-*Acetoxy*-9//10-*seco*-17-iso-1,3,5(10)-*pregnatriene*-11,20-*dione* (XIV)

In the manner described above (XII) was acylated to give 54 per cent yield of (XIV) m.p. 90–94°. Chromatography over Florisil was necessary to purify the crude material. The analytical sample melted 91–93°; λ_{max}^{EtOH} 268 mμ, a_M 555; 274·5 mμ, a_M 540. ν_{max}^{Nujol} 1748, 1694, 1605, 1584, 1494, 1214 cm^{-1}.

Anal. Found: C, 74·69, 74·55; H, 8·10, 8·20.

3-*Methoxy*-9//10-*seco*-1,3,5(10)-*pregnatriene*-11,20-*dione* (XV)

To a solution of 2·0 g of (XI) in 15 ml of ethanol warmed to 70° there was added at 5-min intervals 1 ml of sodium hydroxide (10 g NaOH/25 ml H_2O) and 1 ml of dimethyl sulfate. Five additions were made. The solution was poured into water and the methyl ether extracted with methylene dichloride. After washing with water and drying, evaporation of the solvent gave 2·10 g of oily methyl ether (XV) which resisted crystallization.

Oxidation of 3-*methoxy*-9//10-*seco*-1,3,5(10)-*pregnatriene*-11,20-*dione* (XV)

A solution of 5·0 g sodium hydroxide in 100 ml of water was heated to 90° and 1·0 g of (XV) added. A solution of 4·0 g of potassium permanganate in 80 ml of

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water was added in 20 ml portions. Each addition was made when the permanganate color of the previous addition was discharged. Finally 1·0 g portions of potassium permanganate were added until the purple color persisted at 90° for 1 hr. A total of 9·0 g of potassium permanganate was added. Five milliliters of ethanol was added to destroy the excess oxidizing agent. The solution was filtered after 10 g of Celite 545 was added to aid in the filtration. The clear solution was acidified and concentrated to dryness. The residue was triturated three times with 50 ml portions of hot ethyl acetate. The extract was concentrated to dryness. The extraction with ethyl acetate was repeated to give 0·49 g of solids. By alternate recrystallization from ethyl acetate and water a total of 90 mg of 4-methoxyphthalic acid was obtained m.p. 172–174°. The infra-red absorption of this compound was identical with that of a known sample of this acid.*

3-*Methoxy*-9//10-*seco*-1,3,5(10)-*pregnatriene*-11ξ,20ξ-*diol* (XVI)

Five grams of (XI) was dissolved in 150 ml of benzene and added to 300 ml of ether containing 3·0 g of lithium aluminum hydride. After heating under reflux for 1·5 hr the reaction mix was hydrolyzed and worked up in the usual fashion. The oily residue was methylated as described for the preparation of (XV) to give 4·5 g of oily (XVI).

Dehydration studies with compound (XVI)

Three 100 mg samples of methyl ether (XVI) were treated with thionyl chloride-pyridine, sodium bisulfate and BF_3-etherate, respectively. The ultra-violet absorption curves of the crude products were essentially identical with that of the starting compound.

Dehydrogenation studies with compound (XI)

Treatment of 100 mg samples of (XI) with 5 per cent Pd-C at 250–350° for 10–20 min gave oily products whose ultra-violet absorption showed no bands characteristic of naphthalenic compounds.

3-*Hydroxy*-9//10-*seco*-1,3,5(10)-*androstatriene*-11,17-*dione* (XXIII)

(A) *From adrenosterone*. Ten grams of adrenosterone was pyrolyzed at a bath temperature of 350–360° for 50 min. The melt, when cooled, was dissolved in a mixture of benzene and methylene dichloride and chromatographed over 800 g of Florisil. The fraction eluted with Skellysolve B—4 per cent acetone weighed 814 mg (8·1 per cent yield). Recrystallization from ethyl acetate gave 750 mg m.p. 208–211°; $[\alpha]_D + 85°$; λ_{max}^{EtOH} 281 mμ, a_M 2,250, flex 286 mμ; ν_{max}^{Nujol} 3250, 1735, 1690, 1620, 1590, 1500 cm^{-1}.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75·97; H, 8·05. Found: C, 75·86, 75·88; H, 7·77, 7·66.

(B) *From* 1-*androstene*-3,11,17-*trione*. Pyrolysis of 1·0 g of 1-androstene-3,11,17-trione as described above yielded 135 mg of crude (XXIII) which when recrystallized from ethyl acetate melted 209–212°. The infra-red absorption curve of this material was identical with that from A above.

* We are indebted to Dr. H. Shechter of the Ohio State University for an authentic sample of 4-methoxyphthalic acid.

(C) *From* 1,4-*androstadiene*-3,11,17-*trione*. In a similar manner pyrolysis of 0·5 g of 1,4-androstadiene-3,11,17-trione yielded 100 mg of the seco steroid (XXIII) m.p. 210–214°.

Acknowledgements—The authors are indebted to L. M. Reineke and associates for papergram analyses; to Dr. J. L. Johnson, J. E. Stafford and Mrs. G. S. Fonken for spectroscopic studies; to W. A. Struck and associates for microanalyses and optical rotations; to V. R. Shellman for technical assistance; and to Professor M. S. Newman for valuable suggestions in the course of this work.

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INTERMEDIATE FOR STEROID SYNTHESES

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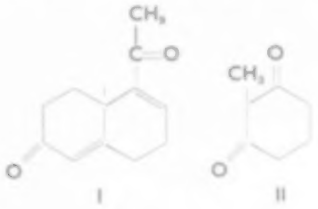
(Received 10 *April* 1957)

Abstract—The synthesis of 1-acetyl-6-oxo-8a-methyl-3,4,6,7,8,8a-hexahydronaphthalene, I, is described.

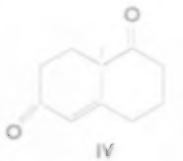
INTEREST in a practical synthesis of cortisone and other cortical hormones prompted this investigation, the first objective of which was the synthesis of 1-acetyl-6-oxo-8a-methyl-3,4,6,7,8,8a-hexahydronaphthalene, I.



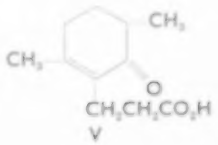
I II

$CH_3\text{-}CO\text{-}CH_2CH_2N(C_2H_5)_2$
III

$CH_3COCH\,[CH_2N(C_2H_5)_2]_2$
IIIa



IV



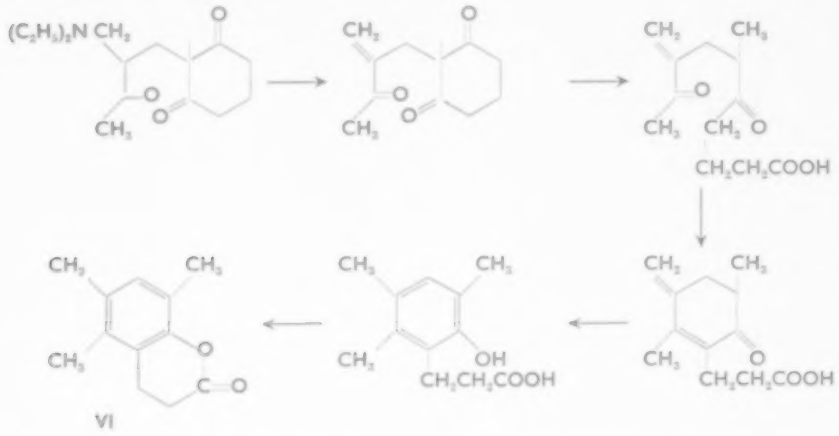
V

This compound could conceivably be used as an intermediate in many ways for building up the steroidal skeleton containing an 11-oxygenated function. Schemes employing this intermediate have been outlined.[1]

The starting material was 2-methyl-1,3-*cyclo*hexanedione (II) which was made by cyclization of methyl 5-oxoheptanoate in 82 per cent yield. This keto ester was prepared in 75–80 per cent yield by the reaction of γ-carbomethoxybutyryl chloride with ethylcadmium. The dione II was also obtained by direct methylation[2,3a,b,c] of dihydroresorcinol, but the yield of pure II was never better than 42 per cent. The alkylation of II with methylvinyl ketone or 1-dimethylamino-3-butanone (III), to yield 1,6-dioxo-8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene (IV), in low yield has been reported.[1a,4,5] When II and III react in benzene in the presence of pyridine consistent yields of 60 per cent of IV may be obtained. The conventional method of alkylation of II with the methiodide of III in the presence of sodium methoxide resulted in the formation

[1] (a) C. A. Friedman and R. Robinson *Chem. and Ind.* 777, 1117 (1951).
(b) S. Swaminathan and M. S. Newman U.S. Pat. **2,** 673, 872 (1954).
[2] Stetter and Dierichs *Ber. Dtsch. Chem. Ges.* **85,** 61 (1952).
[3] (a) H. Smith *J. Chem. Soc.* 803, (1953), (b) E. G. Meek, J. H. Turnbull, W. Wilson *Ibid.* 811 (1953); (c) H. Born, R. Pappo, and J. Szmuskovicz *Ibid.* 1779 (1953).
[4] P. Wieland and K. Miescher *Helv. Chim. Acta.* **33,** 2215 (1950).
[5] H. L. Wendler, H. L. Slates, and M. Tishler *J. Amer. Chem. Soc.* **73,** 3816 (1951).

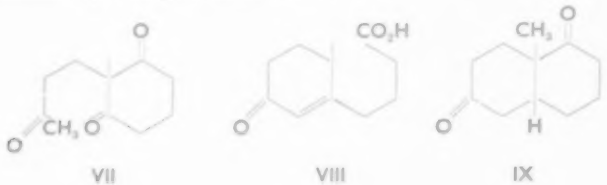
of three products: neutral IV obtained in low yield and identified as the bis-2,4-dinitrophenylhydrazone, and two acidic products having the formulas $C_{11}H_{16}O_3$ and $C_{12}H_{14}O_2$. The former has since been proved[5] to be *β*-(2,5-dimethyl-6-keto-1-*cyclo*hexen-1-yl)propionic acid (V) and the latter could conceivably be VI arising from alkylation of II by the bis-Mannich base, IIIa, present as an impurity, followed by the sequence of reactions indicated below:



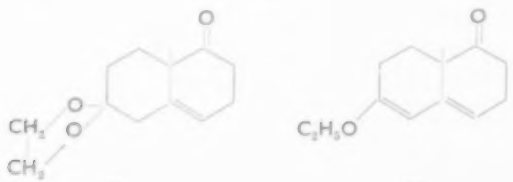
VI

A similar case of formation of byproduct from a bis-Mannich base has been reported.[6]

The reaction of methyl vinyl ketone with II in the presence of Triton B furnished in 35 per cent yield the triketone[7] VII which could also be cyclized by means of a mixture of pyridine and diethylamine in benzene to give IV in 62 per cent yield. Compound IV when treated with dilute alkali underwent cleavage to *γ*-(6-methyl-3-oxo-1-*cyclo*hexen-1-yl)-butyric acid, VIII.



VII VIII IX



X XI

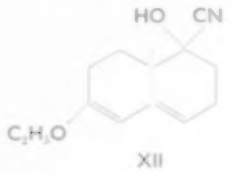
Hydrogenation of IV gave the saturated diketone *cis*-1,6-dioxo-8a-methyl-1,2,3,4,-4a,5,6,7,8,8a,-decahydronaphthalene, IX. The *cis* configuration was indicated

[6] A. L. Wilds and C. H. Shunks *J. Amer. Chem. Soc.* **65**, 471 (1943).

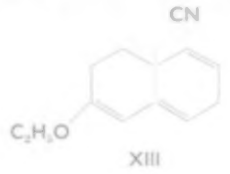
[7] Friedman and Robinson (*loc cit.*) have assigned this structure to the product with m.p. 47–48·5° encountered in the alkylation of II with the methiodide of III. We believe, however, this product to be the isomeric compound V whose structure has been established by Wendler *et al.* (ref. 5).

because an apparently identical compound has been prepared[8] through a Diels-Alder reaction between 2-methoxybutadiene and 2-methyl-2-*cyclo*hexen-1-one followed by hydrolysis. Treatment of IV with ethylene glycol and p-toluenesulfonic acid gave a ketal formulated as X with the double bond in 4, 4a-position in accordance with recent work.[9] With ethyl orthoformate, IV gave the enol ether XI in excellent yield.

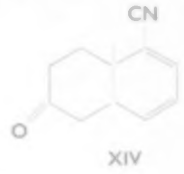
The synthesis of I was attempted in two different ways starting with XI. This enol ether when treated with hydrogen cyanide in the presence of triethylamine gave a mixture of the epimeric cyanohydrins, represented by XII, in 50–55 per cent yield. The latter was dehydrated with a mixture of pyridine and phosphorus oxychloride to give a 52 per cent yield of 1-cyano-6-ethoxy-8a-methyl-3,7,8,8a-tetrahydronaphthalene XIII. This unsaturated nitrile was then treated with methylmagnesium bromide; however, there was no evidence of formation of the desired ketone I, and from the



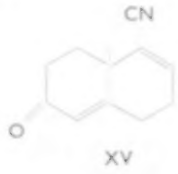
XII



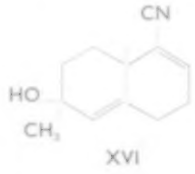
XIII



XIV

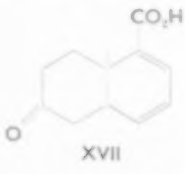


XV

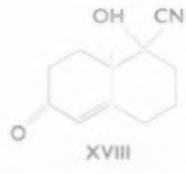


XVI

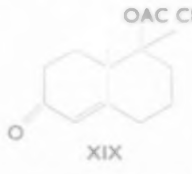
reaction mixture there was isolated after acidification a small amount of a tertiary alcohol, probably XVI, and a keto nitrile. This keto nitrile, which was obtained in better yield (62 per cent) by direct treatment of XIII with alcoholic hydrochloric acid, formed an orange 2,4-dinitro-phenylhydrazone and showed absorption at 289 mμ ($\log_{10}$ ε2·1). This evidence supports structure XIV rather than XV and other possible alternate structures. Alkaline hydrolysis of XIII or the keto nitrile gave the unsaturated acid XVII with absorption at 286 mμ ($\log_{10}$ ε3·52). This unsaturated acid, when treated with oxalyl chloride, lost a molecule of water to give a compound, probably a lactone, which, however, proved unreactive towards dimethyl cadmium. Further attempts in the same direction sought to utilize the fact that IV reacted directly and quantitatively with hydrogen cyanide to yield a mixture of the epimeric cyanohydrins, XVIII. This mixture resisted all attempts at dehydration by a variety of reagents, the



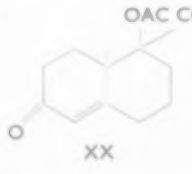
XVII



XVIII



XIX



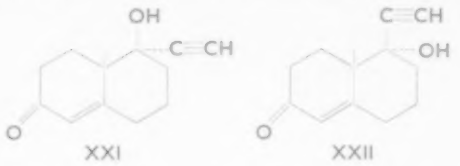
XX

product isolated in most cases being the parent diketone, IV. With *iso*propenyl acetate, XVIII furnished a single acetoxy keto nitrile XIX in good yield. Prolonged

[8] I. N. Nazarov and O. Bergel'son *Zk. Obechei. Khim.* **20,** 648 (1950); *C.A.* **44,** 8913 (1950).
[9] G. I. Poos, C. E. Arth, R. E. Beyler and L. H. Sarett *J. Amer. Chem. Soc.* **75,** 422 (1953).

hydrolysis of XIX with acid led only to the amide XX; the acid apparently was not formed.

From the reaction of XI with potassium acetylide in tertiary amyl alcohol, a mixture of the epimeric ethynyl alcohols XXI and XXII was obtained in 35–40 per cent yield in a ratio of 5:1 respectively. Structure XXI was assigned to the higher melting, less



XXI XXII

soluble isomer. The ultra-violet and infra-red absorption data leave no doubt as regards the structures of the ethynyl alcohols, previously reported as liquids, obtained by reacting IV with sodium acetylide in liquid ammonia. A byproduct isolated in the preparation of the above ethynyl alcohols was the acid VIII indicating that XI underwent cleavage to some extent during the reaction.

The action of formic acid on XXI resulted largely in epimerization to XXII. The desired ketone, I, isolated as the dioxime, was formed only in poor yield. The conversion of XXI to I in good yield was tried with a number of reagents but without success. The difficulty we encountered in effecting this conversion, coupled with the fact that we obtained both the epimeric ethynyl alcohols as fairly high melting solids, prompted us to re-examine the nature of the liquid obtained[1(a)] by reacting sodium acetylide with IV and described as the ethynyl alcohol. On repeating this reaction we obtained a 50–55 per cent yield of a liquid product (b.p. 125–130° at 0·1 mm) along with varying amounts of XXI which, however, did not exceed 5 per cent in any experiment. The same liquid, analyzed for $C_{13}H_{16}O_2$, afforded a crystalline dioxime in 52 per cent yield based on the weight of the liquid used, in contrast to the solid ethynyl alcohols XXI and XXII from which no crystalline oxime could be prepared. There was no depression of melting point on admixture of this product with the dioxime of the product obtained after treatment of XXI with formic acid. Evidently, the liquid product referred to is a mixture of products containing at least 45 per cent of the desired ketone 1, probably formed by isomerization of the intermediate ethynyl alcohols during acidification of the reaction mixture. The dioxime when decomposed with pyruvic acid gave I in 85 per cent yield.

We wish to thank the Upjohn Company, Kalamazoo, Michigan, for their generous support of this research.

EXPERIMENTAL*

1-*Diethylamino*-3-*butanone*

Method A. 1-Diethylamino-3-butanone was prepared according to the method of Wilds and Shunk[6] from acetone, formaldehyde, and diethylamine hydrochloride. Since the yields of the material were quite erratic, procedure (*B*) was followed.

Method B. To a stirred cooled (ice bath) mixture of 160·9 g of diethylamino (2·2 moles) and 4·5 ml of glacial acetic acid were added dropwise 140·3 g (2·00 moles) of methyl

* All of the compounds described gave correct analytical values but since many have been described[4,5] since this work was completed we have omitted duplications. Analyses are given where differences in m.p appear.

vinyl ketone. Stirring was continued for 2 hr while the temperature of the solution was allowed to rise to 27°. After extraction with 50 per cent potassium hydroxide solution and washing with water the dried solution was fractionally distilled through a 10 in. Vigreaux column. Following a forerun of volatile material with an amine-like odor, there were obtained 195·4 g (68 per cent) of colorless liquid, b.p. 69–73°/16 mm.

2-*Methyl*-1,3-cyclo*hexanedione*. II

Method A. To a solution of 90 g of sodium in 1 l. of absolute methanol was added slowly 430 g of dihydroresorcinol[10] (3·84 moles). Gentle reflux was maintained as 650 g of methyl iodide was added over a period of 2 hr. After standing at 25° overnight, 130 g of long white needles of II, m.p. 208–210°, were obtained. Concentration of the remaining solution afforded an additional 73 g of material of the same melting point. The combined fractions, 203 g (42 per cent) were used directly in the next step.

Methyl 5-oxoheptanoate[11]

Method B. To a cooled solution of ethylmagnesium bromide, prepared from 109 g of ethyl bromide and 24·5 g of magnesium in 500 cm³ of anhydrous ether, were added 98 g of anhydrous cadmium chloride during 20 min. After the addition was over, the mixture was stirred for an additional period of 45 min at room temperature. Ether was distilled rapidly from the stirred mixture until distillation slowed down and a nearly dry, dark semisolid remained. To this were added 500 ml of thiophene-free benzene and the benzene suspension was well stirred. A solution of 82·5 g of *v*-carbomethoxybutyryl chloride in 125 ml of benzene was added dropwise. After completion of the addition, the mixture was refluxed with stirring for 30 min and then decomposed with ice and 15 per cent sulfuric acid. After washing with bicarbonate and saturated salt solutions the solvents were stripped. Distillation afforded 61 g (77 per cent) of ester, b.p. 96–97° at 8 mm n_D^{20} 1·4325.

The cyclization of 76·5 g of this ester[12] gave 48 g (79 per cent) of II, m.p. 207–210°.

1,6-*Dioxo*-8a-*methyl*-1,2,3,4,6,7,8,8a-*octahydronaphthalene* (IV)

A mixture of 25·2 g of II, 17 ml of pyridine, 34 g of 1-diethylamino-3-butanone and 250 ml of benzene was refluxed for 18 hr. After cooling, the solution was washed successively with 240 ml of 7·5 per cent hydrochloric acid, two 200 ml portions of water and saturated sodium chloride solution. After removal of solvent, the residual liquid (30 g) was distilled *in vacuo*. The fraction (20 g) with b.p. 109–115° at 0·05 mm solidified when cooled in ice and was crystallized from ether to give 13 g of IV, m.p. 47–48°. An additional 2·5 g of IV was obtained by diluting the ether filtrate with petroleum ether and cooling.

In a subsequent run employing 151·2 g (1·2 moles) of II the reaction product remaining after removal of benzene was solidified by seeding with the product obtained above. The material was then triturated with ether and filtered to give 85 g of IV. The filtrate after concentration gave 100 g of liquid which when distilled *in vacuo* gave 55 g of a fraction, b.p. 109–115° at 0·05 mm and 30 g of a higher fraction, b.p. 115–140° at 0·05 mm. The former yielded 32 g of crystalline IV. The filtrate from this

[10] R. B. Thompson *Org. Syntheses* **27**, 21 (1947).
[11] B. W. Clutterback and H. S. Raper *Biochem. J.* **19**, 393 (1925).
[12] E. E. Blaise and M. Maire *Bull. Soc. Chim.* (4) **3**, 421 (1908).

crystallization was concentrated and the residual liquid (23 g) as well as the higher boiling fraction obtained above were treated with hydroxylamine hydrochloride to give the dioxime of IV. After decomposition with pyruvic acid the dioxime yielded an additional 15–20 g of crystalline IV. The total yield of IV was 61–64 per cent.

The analytical sample of IV,[5] m.p. 47·5–48·5° $\lambda_{max}^{C_2H_5OH}$ 243 mμ, $\log_{10}$ ε4·18 was obtained after two recrystallizations from ether. The i.r. spectrum showed two carbonyl absorptions at 5·82 and 5·98μ in chloroform.

The bis 2,4-dinitrophenylhydrazone[5] of IV melted at 247·5–248·5° (dec.) after crystallization from ethanol-pyridine. A mono-2,4-DNPH was also obtained and crystallized from ethanol-pyridine, m.p. 185·5–186·5°. *Anal.* Calcd. for $C_{17}H_{18}N_4O_5$: C, 57·0; H, 5·1; N, 15·6 Found: C, 56·7; H, 5·2; N, 16·0.

The dioxime of IV was crystallized from methanol and melted at 199–200°. *Anal.* Calcd. for $C_{11}H_{16}N_2O_2$: C, 63·4, H, 7·7; N, 13·5. Found: C, 63·5; H, 7·6; N, 13·8.

Regeneration of IV *from its dioxime*

A mixture of 1 g of the dioxime, 5 ml of acetic acid, 10 ml of water and 2·3 g of pyruvic acid was refluxed for 2 hr and diluted with 20 ml of water. After neutralization with 10 g of sodium bicarbonate, the solution was extracted with ether. The ether extract after washing with saturated sodium chloride solution and drying over anhydrous sodium sulfate was concentrated to give 0·7 g (82 per cent) of crystalline IV.

Cis-1,6-*Dioxo*-8a-*methyl*-1,2,3,4,4a,5,6,7,8,8a-*decahydronaphthalene* (IX)

A solution of 0·5 g of IV in 25 ml of absolute alcohol was hydrogenated at 40 lb/in^2 in the presence of 0·2 g of 1 per cent palladized calcium carbonate for 30 min at 27°. After removal of the catalyst, and concentration of the filtrate to 5 ml, 440 mg (88 per cent) of small white crystals, m.p. 63–64°, was obtained. The analytical sample, obtained by recrystallization from ether-petroleum ether, b.p. 35–40° (Skellysolve F) melted at 64·5–65·5°, $\lambda_{max}^{C_2H_5OH}$ 288 mμ, $\log_{10}$ ε1·59.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73·3; H, 9·0. Found: C, 73·3; H, 8·8. The disemicarbazone[8] melted at 219–222°.

2-*Methyl*-2-(3′-*oxobutyl*)-1,3-cyclo*hexanedione*, VII

A mixture of 7·6 g (0·06 mole) of II, 6 ml of 85 per cent methyl vinyl ketone,* 35 ml of methanol, and 0·8 ml of 40 per cent Triton B (quaternary ammonium hydroxide base) was refluxed for 7 hr. The methanol was removed by distillation and the residual liquid was poured into 50 ml of water acidified with 1·6 ml of 1·5 N hydrochloric acid, and extracted with ether. The extract was washed with 5 per cent sodium bicarbonate solution, followed by saturated sodium chloride solution. After drying and removal of solvent, the residue was distilled *in vacuo* to give 4·1 g (35 per cent) of VII, b.p. 114–116° at 0·1 mm. Treatment with hydroxylamine hydrochloride in pyridine-methanol gave a trioxime, m.p. 181–182°, after two crystallizations from methanol.

Anal. Calcd. for $C_{11}H_{19}N_3O_3$: C, 54·8; H, 7·9; N, 17·4. Found: C, 55·2, H, 8·1; N, 17·3.

Cyclization of 1·96 g of VII in the presence of diethylamine and pyridine afforded IV, m.p. and mixed m.p. 46–48°, in 62 per cent yield.

* We are indebted to the Du Pont Company for generous gifts of methyl vinyl ketone.

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1-*Oxo*-6-*ethoxy*-8a-*methyl*-1,2,3,7,8,8a-*hexahydronaphthalene*, XI

A mixture of 43·2 g of IV, 41 g of triethyl orthoformate, 240 ml of dry benzene, and 10 ml of 5 per cent anhydrous ethanolic hydrochloric acid was refluxed for 2 hr. The dark mixture was cooled, neutralized with 5 per cent alcoholic sodium hydroxide solution, and taken up in 200 ml of ether. The ether-benzene solution was successively washed with 100 ml of water, 300 ml of 5 per cent sodium hydroxide solution, 100 ml of water, and saturated sodium chloride solution, and then dried over sodium sulfate. Distillation afforded 40 g (80 per cent) of a lemon yellow liquid, b.p. 101–104° at 0·1 mm. The analytical sample, b.p. 103° at 0·1 mm, n_D^{24} 1·5257, $\lambda_{max}^{C_2H_5OH}$ 243 mμ, $\log_{10}$ ε4·17, absorption at 5·82 and 6·1 μ (Sandwich cell), was obtained by redistillation.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75·7; H, 8·8. Found: C, 75·2; H, 9·1.

The oxime was prepared through treatment with an aqueous-alcoholic solution of sodium hydroxide and hydroxylamine hydrochloride. After two crystallizations from methanol, it melted at 132·5–134°.

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70·6; H, 8·7; N, 6·3. Found: C, 70·9; H, 8·4; N, 6·2.

The reaction of 2-*methyl*-1,3-cyclo*hexanedione with* 1-*diethylamino*-3-*butanone methiodide in the presence of sodium methoxide*

To a solution of 5·4 g of sodium methoxide in 25 ml of anhydrous methanol was added a solution of 12·6 g of II in 50 ml of dry methanol. The mixture was stirred and treated with 50 ml of a methanolic solution of 40·9 g of 1-diethylamino-3-butanone methiodide. After stirring at 27° for 4 hr, the mixture was refluxed for 2 hr. It was then concentrated by distillation to 45 ml, diluted with 300 ml of water, and extracted with ether. The aqueous layer containing acidic material and the ether layer containing neutral material were worked up separately.

The ethereal solution was washed successively with dilute hydrochloric acid and saturated sodium chloride, and dried over sodium sulfate. After removal of the ether, distillation afforded 2g of a yellow liquid, b.p. 110–115° at 0·29 mm, which gave a 2,4-dinitrophenylhydrazone, m.p. 249–251°, undepressed by admixture with the bis-2,4-DNPH derivative of IV.

The alkaline aqueous layer remaining after extraction from ether was acidified with dilute hydrochloric acid and the acidified solution was extracted with ether. Distillation yielded 11·5 g of a yellow liquid, b.p. 160–170° at 2 mm. The partially solid distillate was dissolved in the minimum amount of ethanol; on addition of a few drops of water and chilling, 0·99 g of material, m.p. 99–102°, were obtained. After two crystallizations from ethanol, the product melted at 103°, and had $\lambda_{max}^{C_2H_5OH}$ 273 mμ, $\log_{10}$ ε3·01, $\lambda_{max}^{C_2H_5OH}$ 282 mμ, $\log_{10}$ ε3·0. I.r. absorption showed a maximum at 5·68μ (chloroform). This product is probably 3,4-dihydro-5,6,8-trimethylcoumarin, VI.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75·8; H, 7·4. Found: C, 75·7; H, 7·2.

The alcoholic filtrate obtained from the product above was freed of solvent and dissolved in ether. After the usual working up 7 g of a liquid b.p. 130–132° at 0·7 mm, were obtained which solidified completely. A portion[5] of V recrystallized three times from ether-Skellysolve F melted at 47–48°, and had $\lambda_{max}^{C_2H_5OH}$ 242 mμ, $\log_{10}$ ε4·25. I.r. absorption maxima at 5·75 and 5·96 μ (tetrahydrofuran).

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67·3; H, 8·2. Found: C, 67·6; H, 8·1; N.E. Calcd. 196·2; Found: 198·2.

The semicarbazone[5] melted at 195–196° after two crystallizations from absolute ethanol.

Anal. Calcd. for $C_{12}H_{19}N_3O_3$: C, 56·9; H, 7·6; N, 16·6. Found: C, 56·9; H, 7·8; N, 17·0.

The 2,4-dinitrophenylhydrazone[5] melted at 103–104° after two crystallizations from ethanol.

Anal. Calcd. for $C_{19}H_{24}N_4O_6$: C, 56·4; H, 6·0; N, 13·9. Found: C, 56·2; H, 6·1; N, 13·9.

γ-(6-Methyl-3-keto-1-cyclohexen-1-yl)-butyric acid (VIII)

A mixture of 0·5 g of IV and 5 ml of 10% potassium hydroxide was allowed to stand for 20 min at 27°, heated on a steam bath for 5 min, cooled and diluted with 5 ml of water, and acidified. The cloudy suspension was extracted with ether, and the solution worked up as usual. There was obtained in 75 per cent yield the acid, VIII,[5] m.p. 77·5–78·0°, $\lambda_{max}^{C_2H_5OH}$ 238 mμ, $\log_{10}$ ε4·17, i.r. absorption at 5·82 and 5·98 μ (chloroform).

1,6-*Dioxo-8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene-6-ethylene ketal*, X

A mixture of 8·9 g of IV, 3·4 g of ethylene glycol, 110 ml of benzene and 0·25 g of *p*-toluenesulfonic acid was refluxed for 5 hr, after which 75 ml of benzene was removed by distillation. The concentrated reaction mixture was refluxed for 4 hr, cooled, and taken up in ether. On distillation at 0·01 mm in a magnetically stirred Hickman still with bath temperature at 100–115° there was obtained 6·1 g (55 per cent) of X as a lemon-yellow liquid having i.r. absorption maxima at 5·85, 6·0, and 6·16 μ (Sandwich cell).

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 70·2, H, 8·2. Found: C, 70·2, H, 7·9.

Preparation of 1-hydroxy-1-cyano-6-ethoxy-8a-methyl-1,2,3,7,8,8a-hexahydronaphthalene, XII

A. By reaction with potassium cyanide and glacial acetic acid. To a cooled stirred suspension of 99 g of potassium cyanide in 160 ml of ethanol was added 90 ml of glacial acetic acid followed with a solution of 24·7 g of XI in 100 ml of ethanol. After 3 hr at 0° the reaction mixture was diluted with 480 ml of water and the yellow solid which separated (17 g) was collected and dried. On further dilution with 600 ml of water, there was obtained 3·2 g of the same material; crystallization from ether afforded 13 g (48 per cent) of cyanohydrin, m.p. 145–155°, undoubtedly a mixture of stereoisomers of XII. After three crystallizations from ether, the m.p. rose to 155–158°; $\lambda_{max}^{C_2H_5OH}$ 242 mμ, $\log_{10}$ ε4·3, i.r. absorption maxima at 3·0, 4·59, 6·03, and 6·13 μ (mineral oil, Nujol).

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72·1; H, 8·2; N, 6·0. Found: C, 71·7; H, 8·0; N, 6·2.

B. By reaction with liquid hydrogen cyanide. To 100 ml of cooled and stirred liquid hydrogen cyanide was added five drops of aqueous potassium cyanide and 100 g of XI dropwise. After the addition was complete, the mixture was allowed to stand for 45 min, and the excess hydrogen cyanide was removed by distillation. Crude material (60 g) was collected. On crystallization from ether 55 g (48 per cent) of XII, m.p. 150–156° was obtained.

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1-*Cyano*-6-*ethoxy*-8a-*methyl*-3,7,8,8a-*tetrahydronaphthalene*, XIII

To an ice cold solution of 42 g of XII in 175 ml of pyridine were added dropwise 34 ml of phosphorus oxychloride. The resulting solution was allowed to stand at 27° for 20 hr and then heated on a steam bath for two hours. After cooling, the reaction mixture was poured on ice, acidified with concentrated hydrochloric acid and immediately extracted with ether. On distillation of the ether-soluble material there was obtained 24 g of liquid, b.p. 125–130° at 0·2 mm. In order to insure that the product was free from material arising from hydrolysis of the enol ether the distillate was heated on a steam bath with a mixture of 24 ml of ethyl orthoformate, 250 ml of benzene and 4 ml of 12 per cent alcoholic hydrochloric acid for 2·5 hr. There was obtained 20 g (52 per cent) of XIII b.p. 105–109° at 0·2 mm., $\lambda_{max}^{C_2H_5OH}$ 232 mμ, $\log_{10}$ ε4·08, i.r. absorption at 4·6 μ (Sandwich cell).

Anal. Calcd. $C_{14}H_{17}NO$: N, 6·5 Found: N, 6·3.

Attempted preparation of 1-*acetyl*-6-*oxo*-8a-*methyl*-3,4,6,7,8,8a-*hexahydronaphthalene* (I) *from* XIII

A solution of 5·7 g of XIII in 50 ml of ether was treated with excess methylmagnesium bromide in ether. After 7 hr at reflux with stirring, the mixture was decomposed with 85 ml of 6 N hydrochloric acid. The ethereal layer was concentrated and the residual liquid (4 g) distilled to yield 1·8 g of distillate, b.p. 95–110° at 0·08 mm. I.r. analysis of this material indicated the presence of —OH, —CN and —CO-groups. Crystallization afforded 0·5 g of material, m.p. 69–70°, undepressed by XIV (see below), obtained by hydrolysis of XIII. The liquid remaining in the mother liquor after removal of the crystalline XIV was dissolved in ether and chromatographed over deactivated alumina. The ethereal eluate deposited crystals after concentration and cooling. When crystallized from a mixture of ether and petroleum ether 18 mg of 1-cyano-6-hydroxy-6,8a-dimethyl-3,4,6,7,8,8a-hexahydronaphthalene, XVI, m.p. 92–93° were obtained. The compound had no maxima between 225 and 300 mμ. I.r. maxima were at 2·83, 4·56 and 6·08 μ (chloroform).

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76·7 H, 8·4; N, 6·9. Found: C, 76·9; H, 8·4; N, 6·7.

1-*Cyano*-6-*oxo*-8a-*methyl*-4a,5,6,7,8,8a-*hexahydronaphthalene* XIV

A mixture of 10·5 g of XIII, 50 ml of ethanol, 25 ml of water, and 5 ml of concentrated hydrochloric acid was refluxed for 45 min. After concentration of the mixture *in vacuo*, the residue was diluted with 100 ml of water and extracted with ether. After the usual working up of the ethereal solution, the residue was distilled at 0·1 mm in a Hickman still, giving 5·67 g (62 per cent) of product, with the bath temperature at 92-96°. The distillate solidified, and after two crystallizations from ether-Skellysolve F, yielded XIV, m.p. 69–70°, $\lambda_{max}^{C_2H_5OH}$ 289 m, $\log_{10}$ ε2·1. I.r. absorption maxima at 4·75, 5·84, and 6·04 μ (chloroform).

Anal. Calcd. for $C_{12}H_{13}NO$; C, 77·0; H, 7·0; N, 7·5. Found: C, 76·9; H, 6·8 N, 7·7.

The orange 2,4-dinitrophenylhydrazone of XIV melted at 161·5–162·5° after crystallization from ethyl acetate-ethanol.

Anal. Calcd. for $C_{18}H_{17}N_5O_4$: C, 58·8; H, 4·7; N, 19·1. Found: C, 58·2; H, 4·7; N, 18·6.

6-*Oxo*-8a-*methyl*-4a,5,6,7,8,8a-*hexahydro*-1-*naphthoic acid*, XVII

A mixture of 6 g of XIII, 40 ml of ethylene glycol, 5 g of sodium hydroxide, and 10 ml of water was refluxed for 8 hr. After cooling, the mixture was poured into water and extracted with ether to remove unreacted nitrile; the aqueous layer was acidified with dilute sulfuric acid and heated on a steam bath for 10 min. The solution was filtered while hot, and on cooling, 0·5 g of crystals was deposited. Ether extraction of the filtrate afforded 1·05 g of material. The combined fractions were crystallized from ethanol to give 1·1 g (19 per cent) of the acid XVII, m.p. 158–159°, $\lambda_{max}^{C_2H_5OH}$ 286 mμ, $\log_{10}\varepsilon$ 3·52. I.r. absorption maximum at 5·88 μ (Nujol).

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69·9; H, 6·8. Found: C, 70·0, 70·1; H, 7·2, 7·0.

The same acid was obtained in comparable yields by hydrolysis of XIV under similar conditions.

Lactonization (?) of XVII *and reaction with methylcadmium*

A mixture of 1 g of 6-oxo-8a-methyl-4a,5,6,7,8,8a-hexahydro-1-naphthoic acid XVII, 3 ml of oxalyl chloride and 20 ml of benzene was kept at 27° for 3 hr. Excess benzene and oxalyl chloride were removed *in vacuo*, and the residual solid was dissolved in 12 ml of benzene. To this solution was added an ethereal solution of methylcadmium (0·0135 mole). The reaction mixture was refluxed for 2 hr and then treated with dilute sulfuric acid. Ether extraction and concentration afforded 0·6 g (64 per cent) of crystalline product, which after two crystallizations from ether melted at 119·0–120·5°. The material was judged to be a lactone, from the i.r. absorption maximum at 5·55 μ. When the acid XVII was heated and sublimed *in vacuo*, the same compound was formed.

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76·6; H, 6·4. Found: C, 76·6, 76·8; H, 6·4, 6·3.

1-*Cyano*-1-*hydroxy*-6-*oxo*-8a-*methyl*-1,2,3,4,6,7,8,8a-*octahydronaphthalene*, XVIII

To an ice-cold solution of 40 g of IV in 70 ml of liquid hydrogen cyanide was added five drops of aqueous potassium cyanide solution. After the mixture had stood at 27° for 30 min the excess hydrogen cyanide was removed by distillation. The residue which solidified on cooling was collected, washed with water, and dried. The yield of crude cyanohydrin was quantitative. After crystallization from ether-methanol or from chloroform five times, XVIII was obtained as a mixture of stereoisomers, m.p. 115–120°, $\lambda_{max}^{C_2H_5OH}$ 244 mμ, $\log_{10}\varepsilon$ 4·13, i.r. absorption maxima at 3·0, 6·01, and 6·15 μ (Nujol).

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70·2; H, 7·4; N, 6·8. Found: C, 70·4, 70·2; H, 7·4, 7·1; N, 6·9, 7·0.

1-*Acetoxy*-1-*cyano*-6-*oxo*-8a-*methyl*-1,2,3,4,6,7,8,8a-*octahydronaphthalene*, XIX

A mixture of 5 g of XVIII, 4 ml of *iso*propenyl acetate, and 10 mg of *p*-toluenesulfonic acid was heated on a steam bath for 30 min. The mixture was clear initially, but solid material appeared as the reaction progressed, and the mass was solid when the heating period was over. After crystallization from alcohol, 5·1 g (85 per cent) of product, m.p. 203–207° was obtained; recrystallization from alcohol yielded the analytical sample, m.p. 208–210°; i.r. absorption maxima at 5·68, 5·96, and 6·12 μ (Nujol).

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68·0; H, 6·9; N, 5·7. Found: C, 68·1; H, 7·0; N, 5·7.

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1-*Acetoxy*-6-*oxo*-8a-*methyl*-1,2,3,4,6,7,8,8a-*octahydro*-1-*naphthoic amide*, XX

A mixture of 2·5 g of XIX and 15 ml of concentrated hydrochloric acid was refluxed for 12 hr. Excess acid was removed *in vacuo*, and the residue was extracted with boiling acetone. The acetone solution afforded 0·8 g of material m.p. 228–231°, the acetone-insoluble residue was treated with sodium carbonate solution and the alkali-insoluble portion was crystallized from ethanol to give an additional 0·41 g of material m.p. 234-237°. The combined crops (46 per cent) were crystallized twice from ethanol to give crude XX, m.p. 240–242°, i.r. maxima at 3·08, 5·83 and 5·93 μ (Nujol).

Anal. Calcd. for $C_{14}H_{19}NO_4$: C, 63·4; H, 7·2; N, 5·3. Found: C, 62·9; H, 7·9; N, 5·9.

1-*Ethynyl*-1-*hydroxy*-6-*oxo*-8a-*methyl*-1,2,3,4,6,7,8,8a-*octahydronaphthalene*, XXI and XXII

Purified and dried acetylene was bubbled through a stirred mixture of anhydrous ether (100 ml) and a solution of 4 g of potassium in 70 ml t-amyl alcohol cooled in ice. After 2 hr, a solution of 20·6 g of freshly distilled XI in 100 ml of anhydrous ether was added over a period of 1 hr. The dark red reaction mixture was allowed to stand overnight in the ice-bath with continued passage of acetylene and stirring. After treatment of the mixture with 200 ml of 6 per cent hydrochloric acid, the ether layer was separated and combined with an additional ethereal extract of the aqueous layer. The combined extracts were washed twice with 150 ml portions of 5 per cent potassium carbonate solution, followed by water and sodium chloride solution. After drying, the solution was concentrated to a volume of 40 ml when crystals were deposited. After chilling, collecting, and washing the material with cold ether, 8·2 g (40 per cent) of light tan crystals, m.p. 140–170°, was obtained. Two crystallizations of this material from alcohol gave 6·6 g of large white prisms, m.p. 170–172°; this represented a yield of 32 per cent of the alcohol XXI. The analytical sample, m.p. 171·5–172·5°, $\lambda_{max}^{C_2H_5OH}$ 240 mμ, 316 mμ, $\log_{10} \varepsilon$ 4·14, 1·76, was obtained through two more crystallizations from alcohol. I.r. absorption maxima at 2·99, 3·08, 4·79, and 6·07 μ (Nujol).

From the mother liquors from crystallizations of the ethynyl alcohol, XXI, there were obtained 1·3 g of white crystals of the isomeric alcohol, XXII, m.p. 145–147°, $\lambda_{max}^{C_2H_5OH}$ 240 mμ, $\log_{10} \varepsilon$ 4·16. i.r. absorption maxima at 2·99, 3·08, 4·79, and 6·07 μ (Nujol).

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76·4; H, 7·9. Found: (172° isomer) C, 76·4; 76·3; H, 7·8, 7·8. (147° isomer) C, 76·1, 76·3, H, 7·6, 7·7.

The reddish purple 2,4-dinitrophenylhydrazone of XXI melted at 221·5–222·5° after two crystallizations from ethyl acetate-alcohol. The deep red 2,4-DNPH of XXII melted at 195–198° after crystallization from alcohol.

Anal. Calcd. for $C_{19}H_{20}N_4O_5$: C, 59·4; H, 5·3; N, 14·6. Found: (DNPH of XXI) C, 59·7; H, 5·4 (DNPH of XXII) C, 59·3; H, 5·4; N, 14·6.

Working up of the original potassium carbonate extract, by acidifying and extracting with ether, afforded 5·6 g of a product which after crystallization from ether-Skellysolve F melted alone and mixed with authentic VIII at 77–78°.

The reaction of 1-*ethynyl*-1-β-*hydroxy*-6-*oxo*-8a-*methyl*-1,2,3,4,6,7,8,8a-*octahydronaphthalene*, XXI, *with formic acid.*

A solution of 4·5 g of XXI in 20 ml of 92 per cent formic acid was refluxed for 1 hr. The excess formic acid was then removed by distillation *in vacuo* and the dark brown

residue was taken up in 150 ml of ether. The ethereal solution was washed successively with 100 ml. of 2 per cent potassium carbonate solution and saturated sodium chloride solution. After drying over sodium sulfate, the ether solution was treated with charcoal (Norite) and concentrated to yield 1·4 g of crystals which after crystallizations from ether containing some ethanol melted at 145–146° alone and mixed with authentic XXII.

The ether filtrate left after separation of XXII was freed of solvent and the residual tarry liquid treated with hydroxylamine hydrochloride in pyridine and methanol. A small amount of the dioxime of I, m.p. 200–202°, was obtained.

In a subsequent similar run with 2·8 g of XXI, the crude liquid left after separation of XXII was chromatographed over deactivated alumina. Elution with ether afforded a small amount of liquid which solidified on cooling. After crystallization from a mixture of ether and petroleum ether, the product (5 mg) melted at 92–93° and was presumably I.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76·4; H, 7·9. Found: C, 76·7; H, 8·0.

The amount available of this material was quite small and no further work was done to characterize it.

The reaction of sodium acetylide with IV

Dry acetylene was bubbled into approximately 200 ml of liquid ammonia in a 500 ml three necked flask equipped with a gas inlet tube and a mechanical stirrer, while 2·3 g of sodium was added over a period of 20 min. The flow of acetylene was then reduced and a solution of 17·8 g of IV in 100 ml of dry ether was added over a period of 1 hr. After this addition was completed, the reaction mixture was allowed to stand for 20 hr. The mixture was then decomposed with 100 ml of ice-cold water and acidified with dilute hydrochloric acid. After washing with alkali and drying, the ether was removed and the residue distilled to yield 9–10 g of a viscous yellow distillate, b.p. 125–130° at 0·1 mm. A portion was redistilled and analyzed.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76·4; H, 7·9. Found: C, 76·6, 76·4; H, 7·9, 7·9.

The distillate obtained above (9 g) when triturated with ether and cooled, deposited 0·5 to 0·7 g of XXI, m.p. and mixed m.p. with authentic XXI, 171–172°. The filtrate was freed of ether and heated for 15 min with a mixture of 7·5 g of hydroxylamine hydrochloride, 25 ml of absolute ethanol and 20 ml of pyridine. The dioxime (4·7 g) of I crystallized after diluting the reaction mixture with water and cooling. After a crystallization from ethanol, it melted at 200–202° alone and mixed with the dioxime of the product of reaction of formic acid with XXI.

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66·6; H, 7·7; N, 12·0. Found: C, 66·9, 66·9; H, 7·9, 7·7; N, 11·6, 11·8.

1-*Acetyl*-6-*oxo*-8a-*methyl*-3,4,6,7,8,8a-*hexahydronaphthalene*, I

A mixture of 2 g of the dioxime obtained above, 5 ml of pyruvic acid, 10 ml of acetic acid and 20 ml of water was refluxed for 1 hr. The reaction mixture was diluted with 100 ml of water, neutralized with sodium carbonate and extracted twice with ether. The combined ether extracts were washed with saturated sodium chloride solution and dried over sodium sulfate. On distillation there was obtained 1·5 g of I, b.p. 85–88° at 0·002 mm., $\lambda_{max}^{C_2H_5OH}$ 246 mμ, $\log_{10}$ ε3·91. i.r. absorption peaks at 5·85, 6·0, and 6·17 μ.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76·4; H, 7·9. Found: C, 76·6, 76·4; H, 7·9, 7·9.

Tetrahedron, 1958, Vol. 2, pp. 100–115. Pergamon Press Ltd., London

SYNTHESES DE SUBSTANCES POLYCYCLIQUES—IX*

OBTENTION D'α-DECALONES SUBSTITUEES PAR CONDENSATION DIENIQUE

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Résumé—L'(acétoxy-1-vinyl)-1-*cyclo*hexène a été préparé par action de l'acétate d'*iso*propényle sur l'acétyl-1-*cyclo*hexène. Ses condensations avec différents diénophiles (anhydride maléique, quinone, acrylate de méthyle, anhydride citraconique) ont été réalisées. L'hydrolyse des produits d'addition formés a permis l'obtention d'α-décalones substituées dont la configuration stérique a été étudiée.

DE NOMBREUSES synthèses de produits polycycliques apparentés aux stéroïdes font appel à la réaction de Diels-Alder.[1] Pendant longtemps les travaux effectués ont eu pour but l'obtention d'hormones sexuelles ou de substances voisines.[2] Il y a quelques années seulement, Sarett[3] a montré qu'en utilisant un alcoxy-2-butadiène-1,3, il était possible de préparer des composés cycliques transformables en produits carbonylés; d'un autre côté, Acheson et Robinson[4], puis Newman et McPherson[5] ont proposé l'utilisation de diènes possédant une fonction oxygénée en C_2 pour la synthèse de céto-11-stéroïdes.

Il était donc intéressant d'étudier le comportement d'acyloxy- ou d'alcoxy-diènes alicycliques, et un produit convenable, pour une étude préliminaire, est un acyloxy- ou alcoxy-vinyl*cyclo*hexène. Quand nous avons entrepris ce travail, aucun produit de ce genre ne semblait être connu. Depuis, Favorskaya et Fedorova[6] ont décrit la préparation du (méthoxy-1-vinyl)-1-*cyclo*hexène et sa condensation avec des quinones; ensuite Nazarov[7] et Ansell et Brooks[8] ont préparé et condensé avec différents diénophiles l'(acétoxy-1-vinyl)-1-*cyclo*hexène (I). C'est ce dernier produit que nous avons également utilisé, et nous avons pu montrer que ce type de composé offrait des possibilités de synthèse intéressantes.[9]

* VIIIème mémoire. F. Winternitz, M. Mousseron et G. Rouzier *Bull. Soc. Chim. Fr.* 170 (1955).

[1] J. A. Norton *Chem. Reviews* **31**, 319 (1942); L. W. Butz et A. W. Rytina dans R. Adams *Organic Reactions* J. Wiley and Sons, New York, T. 5, p. 136 (1949).

[2] (a) Pour une revue générale, voir: K. Alder et M. Schumacher dans L. Zechmeister *Progrès dans la chimie des substances naturelles* Springer-Verlag, Vienne, T. **10**, p. 1 (1953). (b) I. N. Nazarov et coll. Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk, 439 (1949) et publications suivantes.

[3] L. H. Sarett, R. M. Lukes, G. I. Poos, J. M. Robinson, R. E. Beyler, J. M. Vandergrift et G. E. Arth *J. Amer. Chem. Soc.* **74**, 1393 (1952).

[4] R. M. Acheson et Sir R. Robinson *J. Chem. Soc.* 1127 (1952).

[5] M. S. Newman et J. L. McPherson *J. Org. Chem.* **19**, 1717 (1954).

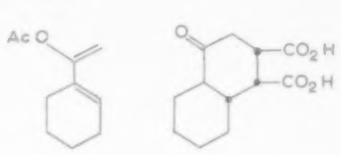
[6] I. A. Favorskaya et L. V. Fedorova, Zh. obshch. Khim., **24**, 242 (1954), *Chem. Abs.* **49**, 4538 (1955); Zh. obshch. Khim., **25**, 1477 (1955), *Chem. Abs.* **50**, 4883 (1956).

[7] I. N. Nazarov, V. F. Kucherov, V. M. Andreev et G. M. Segal Dokl. Akad. Nauk. S.S.S.R. **104**, 729 (1955); *Chem. Abstr.* **50**, 11304 (1956).

[8] (a) M. F. Ansell et G. T. Brooks *Chem. and Ind.* 916 (1955); (b) M. F. Ansell et G. T. Brooks *J. Chem. Soc.* 4518 (1956).

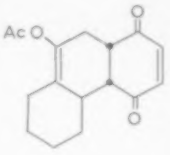
[9] F. Winternitz et C. Balmossière *Bull. Soc. Chim. Fr.* 6, 767, 1393 (1955); 248 (1956); 108, 625 (1957); M. Mousseron, F. Winternitz et C. Balmossière *C. R. Acad. Sci., Paris* **243**, 1328 (1956).

Nous avons préparé l'(acétoxy-1-vinyl)-1-*cyclo*hexène (I) par action de l'acétate d'*iso*propényle sur l'acétyl-1-*cyclo*hexène en présence d'acide sulfurique concentré.[10] La structure du produit obtenu a été confirmée par le spectre d'absorption ultra-violet qui présente un maximum à 232 mμ, ce qui est exactement la valeur calculée par les règles de Woodward.[11]

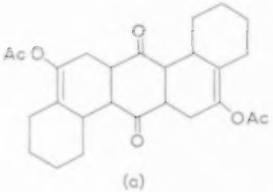


I

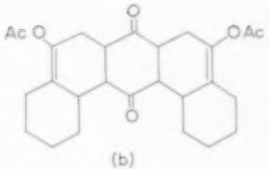
II



III



(a)



(b)

IV

Le diène (I) donne facilement un produit d'addition maléique, qui est hydrolysé en acide oxo-4-décahydronaphtalènedicarboxylique-1,2 (II). D'après son point de fusion, ce produit est identique au produit de configuration *trans*-syn-*cis** obtenu par Ansell et Brooks.[8]

La quinone s'additionne sur I et conduit suivant les conditions expérimentales, soit au produit d'addition simple, soit au produit d'addition avec deux molécules de diène.

Le premier (III) se forme quand on utilise des quantités équimoléculaires (sa purification est alors laborieuse, car il est souillé de quinone) ou un excès modéré de diène. Il a été identifié au moyen de son spectre ultra-violet, qui est semblable à celui du produit d'addition vinyl-1-*cyclo*hexène + quinone[12] et du produit obtenu par Ansell et Brooks[8b] à partir de la quinone et de (I). La double liaison en C_2—C_3 se laisse aisément réduire par le zinc et l'acide acétique à 20°.

Pour des proportions importantes de diène, c'est (IV) qui est produit dans la réaction. Le faible rendement ne nous a pas permis de décider entre les deux formules possibles (IVa et IVb).

Nous pensons pouvoir attribuer à (III) la configuration anti-*cis* indiquée. En effet nous l'avons obtenu au cours de deux expériences réalisées dans des conditions différentes:

(1) à la température ambiante pendant 72 heures, et le produit obtenu est tout à fait identique par son point de fusion, son comportement à la chaleur et son spectre ultra-violet, à celui préparé par Ansell et Brooks[8] dans des conditions analogues.

* Pour désigner les configurations, nous utiliserons les conventions de Linstead.[13] Les points signifient que les atomes d'hydrogène (ou les méthyls angulaires) se trouvent du côté de la molécule qui fait face au lecteur.

[10] W. Theilheimer *Synthetic Methods of Organic Chemistry* S. Karger, Bâle, T. **8**, 125 et 307 (1954); T. **9**, 79 et 208 (1955).
[11] R. B. Woodward *J. Amer. Chem. Soc.* **64**, 72 (1942).
[12] P. A. Robins et J. Walker *J. Chem. Soc.* 642 (1952).
[13] R. P. Linstead *Chem. and Ind.* **56**, 510 (1937); R. P. Linstead et A. L. Walpole *J. Chem. Soc.* 842 (1939).

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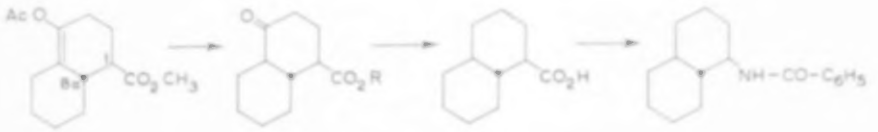
(2) dans l'alcool absolu bouillant, conditions semblables à celles utilisées par Nazarov *et al.*[7]; sur la base du point de fusion (Nazarov indique $F = 121°$) les produits semblent être identiques (nous trouvons pour (III) $F = 117–119°$).

Or, Nazarov attribue à son produit d'addition, qui se forme dans des conditions assez énergiques, la configuration anti-*cis*. Comme nous avons démontré l'identité (point de fusion mélangé) des dérivés obtenus dans les deux expériences, il s'ensuit que le produit d'addition formé dans la première expérience possède aussi la configuration anti-*cis*. Nous avons donc là affaire à un phénomène du même type que celui observé par Lukes *et al.*[14] qui rapportent la formation de la structure "exo" au cours d'une réaction diénique lente effectuée à basse température, alors que les règles d'Alder et Stein[15] laissaient prévoir une structure "endo". Il faut d'ailleurs noter que de nombreux auteurs ont déjà observé que dans des conditions de contrôle thermodynamique de la réaction le produit d'addition obtenu correspond à un complexe intermédiaire possédant une densité minima des doubles liaisons.

Nous avons pu réaliser la condensation de l'acétoxydiène I avec l'acrylate de méthyle de façon satisfaisante dans des conditions énergiques. Il se forme alors le produit d'addition correspondant à la disposition 1–4 des groupements acétoxy et carbométhoxy, et possédant la configuration anti des carbones 1 et 8a. Ces résultats sont en accord avec ce que l'on sait de l'influence exercée par l'emplacement des substituants du diène sur la direction de l'addition[16] et de la diminution rapide de la validité du "principe d'accumulation maximum des doubles liaisons" avec la température, en particulier pour les diénophiles mono fonctionnels, peu réactifs.[16b,17] Nous devons noter que dans des conditions moins énergiques Nazarov obtient le mélange des deux épimères en C_1.



V VI

L'acide décalone-4-carboxylique-1 (V, R = H) qui se forme par saponification du produit d'addition a été identifié par comparaison avec un échantillon authentique préparé selon Novello *et al.*[18] par une réaction de Robinson-Mannich réalisée à partir de l'acétyl-1-cyclohexène (Tableau 1). L'acide cétonique de Novello possède la configuration *trans* des noyaux; par conséquent la saponification de l'acétate d'énol a fourni la configuration *trans*, ce qui était prévisible à cause de la plus grande stabilité thermodynamique de cette configuration (cf. aussi par exemple,).[19] Dans le même cas, Nazarov obtient lui aussi des dérivés de la *trans*-décalone.[7]

[14] R. M. Lukes, G. I. Poos et L. H. Sarett *J. Amer. Chem. Soc.* **74**, 1401 (1952).
[15] K. Alder et G. Stein *Angew. Chem.* **50**, 510 (1937).
[16] (a) K. Alder et W. Vogt Ann. Chem. **504**, 109, 120 (1949). (b) K. Alder, M. Schumacher et O. Wolff Ann. Chem. **504**, 79 (1949).
[17] I. N. Nazarov, V. F. Kucherov et G. Segal, Izvest. Akad. Nauk S.S.S.R. Otdel. khim. Nauk, 1956, 557; *Chem. Abstr.* **51**, 1927 (1957).
[18] F. C. Novello, M. E. Christy et J. M. Sprague *J. Amer. Chem. Soc.* **75**, 1330 (1953).
[19] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler et W. M. McLamore *J. Amer. Chem. Soc.* **74**, 4223 (1952).

La position spatiale du groupement carboxyle dans (V, R = H) a été déterminée par passage à des produits décahydronaphtaléniques connus. Nous avons réduit le carbonyle soit par la méthode de Clemmensen appliquée à l'acide (V, R = H), soit par la méthode de Wolfrom et Karabinos[20] appliquée à l'ester méthylique (V, R = CH_3). Dans les deux cas on obtient un acide décahydronaphtoïque (VI) $F = 96–98°$, qui paraît être l'acide *trans-trans* $F = 102°$ décrit par Dauben.[21] Le point de fusion de l'amide correspondant est nettement inférieur à celui indiqué par cet auteur; ceci est vraisemblablement dû au fait que dans notre cas la sublimation de l'amide a pu provoquer une épimérisation partielle en C_1. Cette hypothèse se trouve confirmée par l'action du nitrite de sodium sur cet amide qui donne un acide de point de fusion abaissé, $F = 65–70°$.

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Tableau I.—Points de fusion

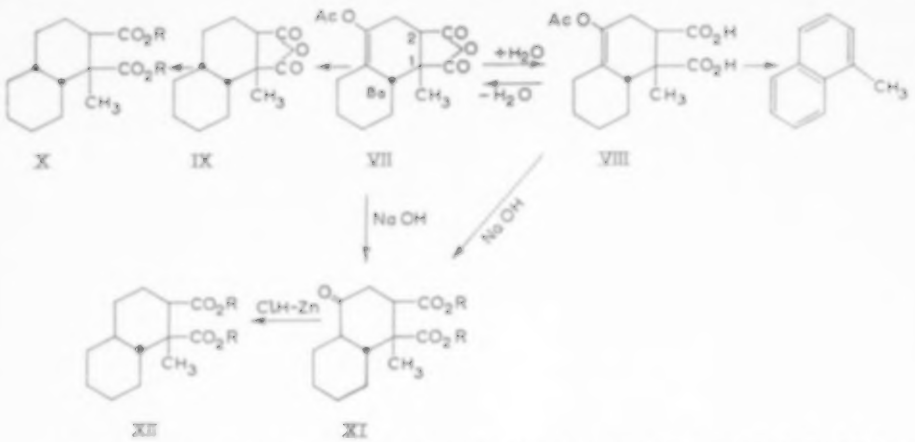
	Acide (V) (R = H)	Acide décalone-4-carboxylique-1	Mélange
Acide	153–154°	151–153°	151–154°
Dinitro-2,4-phénylhydrazone	210–212° déc.	211–214° déc.	211–213° déc.

L'(acétoxy-1-vinyl)-1-*cyclo*hexène se condense également avec l'acroléine et l'acrylonitrile. Les mauvais rendements ne nous ont pas permis d'effectuer l'étude de la structure des produits formés. Ceux-ci ont été identifiés par leurs dinitro-2,4-phénylhydrazones après saponification du groupement acétate d'énol.

La condensation de I avec l'anhydride citraconique conduit probablement au mélange des deux produits d'addition isomères de position du méthyle, possibles. Nous n'avons cependant pas pu réaliser leur séparation quantitative de façon satisfaisante. Toute notre étude a porté sur un produit solide ($F = 142–3°$) qui cristallise par refroidissement du mélange réactionnel. Il possède une structure stéroïde "inversée", c'est-à-dire une structure où le méthyle se trouve en position 1 sur le noyau hydronaphtalénique (VII). Cette position du méthyle a été déterminée par déshydrogénation du diacide-acétate d'énol (VIII), provenant de l'hydrolyse neutre de (VII), en méthyl-1-naphtalène. Malgré plusieurs recristallisations, nous n'avons pas trouvé, pour le picrate du carbure obtenu, ainsi que pour un échantillon authentique, de points de fusion supérieurs à 138°, alors que la littérature indique 141°.[23]

Le diacide acétate d'énol (VIII) redonne l'anhydride de départ par action du NN'-di*cyclo*hexylcarbodiimide.[24] La soude diluée hydrolyse (VII) ou le diacide (VIII) en diacide cétonique (XI, R = H), qui est facilement transformé par le chlorure d'acétyle en l'anhydride correspondant et par le diazométhane en diester méthylique (XI, R = CH_3).

[20] W. L. Wolfrom et J. V. Karabinos *J. Amer. Chem. Soc.* **66**, 909 (1944).
[21] W. G. Dauben, R. C. Tweit et C. Mannerskantz *J. Amer. Chem. Soc.* **76**, 4420 (1954).
[22] W. G. Dauben et E. Hoerger *J. Amer. Chem. Soc.* **73**, 1504 (1951).
[23] R. L. Shriner et R. C. Fuson *Identification of organic Compounds* pp. 259, (3rd Ed.) J. Wiley and Sons, New York (1948).
[24] Pour une revue générale voir H. G. Khorana *Chem. Rev.* **53**, 145 (1953).



La configuration de (VII) en C_1—C_2 est *cis* d'après le "*cis*-Principe" de l'addition diénique. L'isomérisation facile en dérivé *trans* du diacide décahydronaphtalénique (X,R = H), obtenu par la suite, prouve que cette configuration est exacte.

On peut attribuer aux carbones 1 et 8a la configuration anti. En effet, à une température plus élevée (180–190°), c'est le même produit d'addition (VII) qui se forme. Celui-ci semble donc être stable au point de vue thermodynamique. Or, il est bien connu que les dérivés les plus stables thermodynamiquement sont en général

TABLEAU 2.—POINTS DE FUSION

		Produits obtenus par réduction de XI	Produits obtenus par hydrogénation catalytique de VII	Produits de Nazarov
Série cis	diacide	177–178° déc.	180–182° déc.	177,5–178,5° déc.
	anhydride	liq, $Eb_{0,001}$ = 125–130°	129,5–131°	130–131°
C_1—C_2	diester méthylique	60,5–62°	58–59,5°	49–50,5°
Série trans	diacide		224–227° déc.	228–229° déc.
	anhydride		89,5–90°	83,5–84,5°
C_1—C_2	diester méthylique		49,5–50,5°	47–48°

ceux de structure "exo". Nous avons pu confirmer ce point de vue par le passage à des produits synthétisés par Nazarov *et al.* à partir du vinyl-1-*cyclo*hexène et de l'anhydride citraconique,[25] pour lesquels ces auteurs adoptent la structure "exo".

L'hydrogénation de (VII), qui n'est pas réalisable dans les conditions ordinaires, peut être effectuée sous pression (50 kg) en présence de platine. Elle est accompagnée d'hydrogénolyse et l'on obtient un anhydride décahydronaphtalénique (IX), à partir duquel nous avons préparé toute une série de composés dont les points de fusion sont en accord avec ceux indiqués par Nazarov[25] (voir Tableau 2).

[25] I. N. Nazarov, V. F. Kucherov et V. M. Andreev *Bull. Acad. Sci. U.R.S.S. Div. Chem. Sci.* 67, 77 (1955).

Par contre, la réduction du diacide cétonique (XI) par la méthode de Clemmensen ou par la méthode de Wolff-Kishner fournit un diacide saturé (XII, R = H) différent de celui (X, R = H) provenant de l'hydrogénation catalytique de (VII). Les produits que nous avons préparé à partir de (XII, R = H) sont totalement différents de ceux obtenus après hydrogénation catalytique et par conséquent de ceux de Nazarov (cf. Tableau 2). Nous avons en particulier remarqué la très faible réactivité de la fonction ester secondaire du diester (XII, R = CH_3). Celui-ci n'est saponifiable en totalité que dans des conditions très énergiques, avec alors isomérisation partielle en diacide *trans*; dans des conditions moins énergiques on obtient un hémi-ester. Le méthylate de sodium ne produit aucune isomérisation: il se forme un acide ester, qui par action du diazométhane redonne le diester de départ. Ce résultat montre que c'est la fonction ester secondaire, susceptible de subir une stéréoisomérisation sous l'action du méthylate de sodium, qui est peu réactive.

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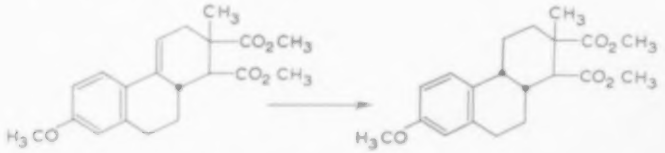
Nous ne pensons pas que les réactions de Clemmensen et de Wolff-Kishner aient pu provoquer une isomérisation en C_1—C_2. En effet, d'une part nous avons affaire aux configurations "exo" les plus stables; d'autre part nous avons traité l'anhydride (IX) et l'acide (X) dans les conditions d'une réaction de Clemmensen sans observer de changement de configuration. Nous avons seulement constaté la grande stabilité et la facilité de formation de l'anhydride (IX).

Les produits (X) et (XII) ne peuvent donc différer que par la configuration des noyaux. Or, on peut raisonnablement attribuer au diacide (XI) la configuration de la *trans*-α-décalone, la saponification de la fonction acétate d'énol ayant donné la configuration la plus stable, comme nous l'avons observé plus haut. On trouve d'ailleurs dans la littérature de nombreux exemples venant appuyer cette affirmation (voir en particulier),[7] qui est également soutenue par un résultat expérimental: le diacide cétonique (XI) reste inchangé par ébullition avec la soude, alors que les dérivés de la *cis*-α-décalone sont isomérisés dans ces conditions en dérivés de la *trans*-α-décalone.

Par conséquent notre acide (XII) provenant de (VII) par hydrolyse alcaline et réactions de Clemmensen ou de Wolff-Kishner possède le noyau de la *trans*-décaline, et les produits obtenus par hydrogénation catalytique de (VII) le noyau de la *cis*-décaline. Il semble donc que la configuration trans adoptée par Nazarov pour les cycles des produits qu'il a préparés devrait être réexaminée.

Enfin à l'appui de notre hypothèse il faut noter que l'on trouve dans la littérature au moins un exemple où la double liaison d'un produit d'addition citraconique de structure "exo" est hydrogénée avec formation d'un produit de configuration *cis*: Heer et Miescher[26] ont montré que le diester méthylique de l'acide anti-*cis*-méthoxy-7-méthyl-2-hexahydro-1,2,3,9,10,10a-phénantrènedicarboxylique-1,2 donne par hydrogénation catalytique dans les conditions habituelles le dérivé octahydro correspondant dans lequel les noyaux B et C possèdent la configuration *cis*: L'extension de ce travail à des cycles plus condensés est poursuivie.



[26] J. Heer et K. Miescher *Helv. Chim. Acta* **32**, 1572 (1949).

PARTIE EXPERIMENTALE

(*Acétoxy*-1-*vinyl*)-1-cyclo*hexène* (I). Vingt-cinq grammes d'acétyl-1-*cyclo*hexène[27] et 75 cm³ d'acétate d'*iso*propényle sont chauffés en atmosphère d'azote en présence de 5 gouttes d'acide sulfurique concentré, de façon à distiller lentement un mélange constitué de l'acétone formée et d'acétate d'*iso*propényle (20–25 cm³ en 4 heures). Après neutralisation par un excès d'acétate de sodium anhydre, on reprend par 250 cm³ d'éther, lave au bicarbonate de sodium, sèche sur sulfate de sodium et fractionne. On obtient 25 g (75%) d'un liquide incolore d'odeur agréable, $Eb_{20} = 110 - 115°$.

Analyse:	$C_{10}H_{14}O_2$,	Calc%	C 72,28	H 8,43
	(166)	Tr	72,65	8,21

Spectre u.v. (alcool): $\lambda_{max} = 232$ mμ, log $\varepsilon_{max} = 4,16$

Indice de saponification:0, 4321 g d'acétate d'énol sont saponifiés par 20 cm³ de potasse alcoolique 0,93 N (30 min à 80°). L'excès de potasse est dosé par l'acide chlorhydrique 1 N (16,1 cm³) en présence de phénolphtaléine.

Trouvé: 173 Calculé: 166

Acide trans-*syn*-cis *oxo* 4-*décahydronaphtalènedicarboxylique*-1,2 (II). Un gramme d'acétate d'énol (I) et 0,6 g d'anhydride maléique sont dissous dans 10 cm³ de benzène déthiophéné. On abandonne une nuit à la température ambiante, puis on porte à à reflux pendant 8 heures. Après évaporation du solvant, le résidu est hydrolysé par un excès d'une solution saturée de carbonate de sodium, à 100° pendant 2 heures. Les produits neutres sont extraits à l'éther, les eaux alcalines acidifiées par l'acide chlorhydrique concentré et les produits acides extraits à l'éther. Après évaporation de l'éther, il reste un résidu solide qui est recristallisé dans l'éther-ligroïne.

Cristaux $F = 190–3°$. Rdt 60%

Analyse:	$C_{12}H_{16}O_5$,	Calc %	C 60,00	H 6,66
	(240)	Tr	59,85	6,69

Ansell et Brooks[8b] indiquent $F = 191–5°$ pour le produit *trans*-syn-*cis*.

Anti-cis-*acétoxy*-9-*dioxo*-1,4-*décahydro*-1,4,4a,4b,5,6,7,8,10,10a-*phénanthrène* (III). (1) A1,08 g de quinone purifiée dans 15 cm³ d'alcool absolu sont ajoutés 4 g (2,4 moles) d'acétoxydiène (I). On abandonne à température ambiante pendant 3 jours, puis dilue avec 45 cm³ d'éther de pétrole et refroidit à 0° pendant un jour. Le produit qui cristallise (Rdt 63%) est essoré et lavé à l'éther de pétrole. Recristallisé dans l'alcool-éther de pétrole. Prismes jaune pâle, $F = 117–119°$. Si le chauffage est continué après la fusion, le produit se resolidifie vers 150–160° et fond à nouveau à 219–221°.

Analyse:	$C_{16}H_{18}O_4$,	Calc %	C 70,05	H 6,61
	(274)	Tr	69,89	6,63

Ansell et Brooks[8b] indiquent $F = 118–120°$, se resolidifie à température plus élevée et fond définitivement à 224°.

Spectre u.v. (alcool):	λ_{max} (mμ)	225	284	346
	log ε_{max}	3,97	2,35	1,92

(2) Trois grammes d'acétate d'énol et 1,95 g de quinone purifiée (1 mole) dans 50 g d'alcool absolu sont portés à reflux pendant 5 heures. Après abandon une nuit à

[27] E. E. Royals et C. M. Hendry *J. Org. Chem.* **15**, 1153 (1950).

température ambiante, on évapore à sec sous vide et le résidu semi solide est recristallisé dans l'alcool-éther de pétrole jusqu'à point de fusion constant. Rendement: 1,1 g (30%) $F = 116,5$–$118°$.

Identique au produit précédent: F (mélange) = 117–120°.

Anti-cis-*acétoxy*-9-*dioxo*-1,4-*dodécahydro*-1,2,3,4,4a,4b,5,6,7,8,10,10a-*phénanthrène*. A 0,15 g de produit d'addition dans 10 cm³ d'acide acétique glacial sont ajoutés par portions 0,15 g de zinc en poudre, à 20°, en agitant. On agite encore 10 min, filtre et évapore à sec. Le résidu solide est épuisé à l'éther de pétrole contenant quelques gouttes d'alcool. Les solutions filtrées et concentrées laissent déposer 0,1 g d'aiguilles blanches, $F = 116$–$117°$. Différent de l'adduct initial (mélange $F = 98$–$103°$).

Analyse:	$C_{16}H_{20}O_4$,	Calc %	C 69,55	H 7,29
	(276)	Tr	69,62	7,28

Produit d'addition double (IV). 0,5 g de quinone et 3,6 g d'acétoxydiène (4,6 moles) en solution dans 5 cm³ de méthanol absolu sont abandonnés deux jours à la température ambiante. Après dilution avec un volume d'éther de pétrole et refroidissement plusieurs heures à 0°, il se forme un précipité qui est recueilli. Recristallisé dans le méthanol-éther de pétrole. Rdt = 0,25 g (12,5%). Poudre cristalline blanche, $F = 238$–$240°$ déc.

Analyse:	$C_{26}H_{32}O_6$,	Calc %	C 70,90	H 7,25
	(440)	Tr	70,60	7,36

Acide trans-*anti-oxo*-4-*décahydronaphtalènecarboxylique*-1 (V). Douze grammes de I, 6,5 g d'acrylate de méthyle et 0,2 g d'hydroquinone sont placés dans un tube en pyrex et chauffés en tube scellé à 160° pendant 15 heures. Le mélange réactionnel est distillé. On obtient 12 g (66%) de produit d'addition $Eb_{0,1} = 118$–$122°$.

Ce produit d'addition brut est saponifié par 10 g de potasse dans 20 cm³ de méthanol, à reflux 5 heures. Après évaporation de la plus grande partie du méthanol, on reprend par de l'eau, extrait à l'éther, décolore les eaux et les acidifie par l'acide chlorhydrique concentré. L'acide qui précipite est extrait à l'éther. Rendement: 7,5 g. $F = 150$–$3°$.
Recristallisé dans l'alcool-cyclohexane. Prismes, $F = 153$–$4°$.

Analyse:	$C_{11}H_{16}O_3$,	Calc %	C 67,34	H 8,16
	(196)	Tr	67,28	8,13

Sel de S-Benzylisothiouronium. $F = 146$–$7°$ (alcool dilué).

Analyse:	$C_{19}H_{26}N_2O_3S$,	Calc %	N 7,73
	(362)	Tr	8,06

Dinitro-2,4-*phénylhydrazone*: Poudre cristalline jaune orangé. $F = 210$–$2°$ déc (alcool).

Analyse:	$C_{17}H_{20}N_4O_6$,	Calc %	N 14,89
	(376)	Tr	15,02

Trans-*anti-oxo*-4-*décahydronaphtalènecarboxylate de méthyle*-1. A une solution éthérée de 4 g d'acide on ajoute par portions, à 0°, un excès d'une solution éthérée de

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diazométhane. Après un contact de plusieurs heures, la solution est évaporée sous vide et le résidu distillé en boules. Rendement 4 g. $Eb_{0,01} = 120°$. Le produit se solidifie lentement par abandon à la température ambiante. Il est purifié par passage sur une colonne d'alumine et élution au benzène. Solide cristallin blanc. $F = 54–55°$.

Analyse:	$C_{12}H_{18}O_3$,	Calc %	C 68,57	H 8,57
	(210)	Tr	68,45	8,70

Dinitro-2,4-phénylhydrazone. Poudre jaune-orangé. $F = 161–2°$ (alcool).

Analyse:	$C_{18}H_{22}N_4O_6$,	Calc %	N 14,36
	(390)	Tr	14,49

Acide trans-*anti-décahydronaphtalènecarboxylique*-1 (VI). (1) Réaction de Clemmensen. A 50 g de zinc amalgamé, 25 cm³ d'acide chlorhydrique concentré et 10 cm³ d'eau sont ajoutés 4 g d'acide cétonique (V, R = H) dans 50 cm³ de toluène et 50 cm³ d'acide acétique. On fait refluer pendant 48 heures au cours desquelles on ajoute 6 portions de 10 cm³ d'acide chlorhydrique concentré. Après le traitement habituel, on obtient un produit pâteux qui est estérifié par le diazométhane. La distillation en boules fournit 3,5 g d'un liquide incolore $Eb_{0,03} = 110°$. Cet ester est saponifié par 20 cm³ de potasse hydroalcoolique à 15% en donnant 3 g d'un solide blanc. Recristallisé dans l'éther de pétrole. $F = 96–8°$.

Analyse:	$C_{11}H_{18}O_2$,	Calc %	C 72,53	H 9,89
	(182)	Tr	71,83	10,10

Amide $F = 206–8°$ (sublimation).

Analyse:	$C_{11}H_{19}NO$,	Calc %	N 7,74
	(181)	Tr	7,70

(2) Méthode de Wolfrom-Karabinos. 2 g d'ester cétonique (V, R = CH_3) sont ajoutés à 5 cm³ d'éthylmercaptan, 0,3 g de chlorure de zinc fraîchement fondu et 0,25 g de sulfate de sodium anhydre, en refroidissant à −5°. On abandonne à 0° pendant 20 heures. Le mélange réactionnel, qui a pris une teinte rose vif, est jeté sur 20 g de glace pilée et extrait à l'éther. Les éthers sont lavés à la soude 10%, à l'eau, séchés sur sulfate de sodium et chassés. L'huile d'odeur nauséabonde qui reste tes traitée par environ 10 g de nickel Raney dans 100 cm³ d'alcool à 70%, au reflux pendant une nuit. On filtre, concentre sous vide et saponifie le résidu huileux. Rendement 1 g. $F = 94–97°$.

Identique (point de fusion et point de fusion mélangé) au précédent.

Trans-*anti-N-Benzoyl-amino*-1-*décahydronaphtalène*. Un gramme d'acide (VI) dans 28 cm³ de chloroforme et 11 cm³ d'acide sulfurique concentré est traité par 0,55 g d'azidure de sodium dans les conditions opératoires décrites par Dauben et Hoerger[22]. Le benzoate, préparé à partir de l'amine brute par la méthode de Schotten-Baumann, est recristallisé plusieurs fois dans l'alcool dilué. $F = 194–5°$. La littérature[21] indique: $F = 195°$.

Condensation de I *avec l'acroléine*. 2,5 g d'acétate d'énol (I) et 1,2 g d'acroléine sont chauffés en tube scellé en présence d'un peu d'hydroquinone, à 140–150° pendant 15 heures. La distillation en boules du mélange réactionnel fournit 0,3 g d'une huile $Eb_{0,1} = 110°$. Après hydrolyse par le carbonate de sodium, à 100°, on fait la dinitro-2,4-phénylhydrazone.

Bis-*dinitro*-2,4-*phénylhydrazone*. $F = 225°$ déc. (alcool).

Analyse: $C_{23}H_{24}N_8O_2$,	Calc %	N 20,74	
(540)	Tr	21,14	

Condensation de I *avec l'acrylonitrile*. 2,5 g d'acétate d'énol (I) et 0,8 g d'acrylonitrile dans 5 cm³ de toluène sont chauffés en tube scellé à 140–150° pendant 15 heures. Rendement 0,3 g. Liquide incolore, $Eb_{0,02} = 115°$. Hydrolysé par le carbonate de sodium saturé, à 100°.

Dinitro-2,4-*phénylhydrazone*. $F = 160–161°$ (alcool)

Analyse: $C_{17}H_{19}N_5O_4$,	Calc %	N 19,63	
(357)	Tr	19,92	

Condensation de I *avec l'anhydride citraconique*. 18,6 g d'acétoxydiène (I) (excès de 40 %) et 9 g d'anhydride citraconique sont chauffés en tube scellé en présence de 0,1 g de pyrogallol, à 110–120°, pendant 21 heures. On abandonne à la température ambiante 24 heures, puis à 0° une nuit. Le précipité cristallin formé est essoré et lavé à l'éther. Rendement: 11,4 g d'anhydride de l'acide anti-*cis*-acétoxy-4-méthyl-1-octahydro-1,2,3,5,6,7,8,8a-naphtalène-dicarboxylique-1,2 (VII), $F = 139–141°$.

Recristallisé dans un peu de benzène. Aiguilles fines et blanches, $F = 142–143°$.

Analyse: $C_{15}H_{18}O_5$,	Calc %	C 64,75	H 6,52
(278)	Tr	64,46	6,36

Anilide-acide. Deux grammes de produit d'addition, 0,7 g d'aniline (1 mole) et 60 cm³ de toluène sont portés à reflux pendant une heure, au cours de laquelle il se forme un précipité blanc. Après refroidissement celui-ci est essoré, lavé avec un peu de méthanol et d'éther de pétrole. Rendement 2,3 g. $F = 220–222°$ déc. Recristallisé dans l'éthanol. Petites et fines aiguilles cotonneuses. $F = 222–224°$ déc. Soluble dans la soude 10 % à froid.

Analyse: $C_{21}H_{25}NO_5$,	Calc %	C 67,92	H 6,73	N 3,77
(371)	Tr	67,83	6,83	3,70

Les eaux-mères du produit solide précédent sont distillées en boules, ce qui permet d'obtenir 3,3 g d'un produit pâteux jaune clair $Eb_{0,06} = 165–170°$. L'hydrolyse alcaline en est effectuée comme pour le solide (voir ci-après). On obtient un produit cristallisé $F = 146–152°$ déc. La recristallisation d'une petite partie dans l'alcool-hexane donne des aiguilles prismatiques.
$F = 179–181°$ déc.

Analyse: $C_{13}H_{18}O_5,H_2O$,	Calc %	C 57,33	H 7,39
(272)	Tr	57,68	7,55

Acide anti cis-*acétoxy*-4-*méthyl*-1-*octahydro*-1,2,3,5,6,7,8,8a-*naphtalènedicarboxylique*-1,2 (VIII). (1) *Forme hydratée*. Un gramme de produit d'addition est dissous dans 25 cm³ d'eau distillée à l'ébullition. On fait bouillir encore 1/2 heure après la dissolution totale. Par abandon une nuit à la température ambiante, il se sépare 0,8 g de cristaux. Recristallisé dans l'acétone diluée.

Ce produit n'a pas de point de fusion net: par chauffage il fond en partie à

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110–115° avec formation de bulles, puis se solidifie immédiatement et fond définitivement à 160–163°.

Analyse:	$C_{15}H_{20}O_6,\frac{1}{2}H_2O$, (305)	Calc %	C 59,01	H 6,88
		Tr	58,75	7,26

Equivalent de saponification-neutralisation. Déterminé sur 0,1706 g d'acide au moyen d'un excès (20 cm³) de potasse aqueuse 0,134 N, par chauffage à 100° pendant une heure, et dosage de l'excès de potasse par l'acide chlorhydrique 0,1 N (9,8 cm³) en présence de phénolphtaléine.

Trouvé = 100,3 Calculé = 101,7

(2) *Forme anhydre*. 1,4 g de produit d'addition sont hydrolysés comme ci-dessus. Après refroidissement à la température ambiante, on extrait à l'éther. Rendement 1,55 g. F = 164–167° déc. Par recristallisation dans l'éther-éther de pétrole on obtient des cristaux incolores, F = 168–169° déc.

Analyse:	$C_{15}H_{20}O_6$, (296)	Calc %	C 60,81	H 6,76
		Tr	61,03	6,84

Equivalent de saponification-neutralisation. Déterminé par la méthode indiquée plus haut. Prise d'essai: 0,2146 g. Potasse alcoolique 0,134 N: 20 cm³. Acide chlorhydrique 0,1 N: 5,3 cm³.

Trouvé = 99,8 Calculé = 98,7

Les deux produits précédents décolorent le brome dans le tétrachlorure de carbone. Leur saponification alcaline donne quantitativement le diacide cétonique (XI, R = H).

Bis-*sel de S-benzylisothiouronium*. Pour le préparer, on a préféré dissoudre l'acide dans le carbonate de sodium dilué au lieu de la soude pour éviter toute saponification. F = 129–131° (brunit) (alcool dilué).

Analyse:	$C_{31}H_{40}N_4O_6S_2$, (628)	Calc %	N 8,91
		Tr	8,40

Anhydrisation de VIII. A 0,1 g d'acide VIII (forme anhydre) en solution dans un mélange de benzène et d'acétate d'éthyle on ajoute 0,07 g de N-N'-dicyclohexylcarbodiimide dissous dans le minimum de benzène. Au bout de quelques dizaines de secondes, il commence à apparaître un précipité. On abandonne 2 heures à la température ambiante, filtre la dicyclohexyl urée et évapore la solution à sec. Le résidu solide est recristallisé dans un peu de benzène. Rendement 0,06 g. F = 142–3°. Mélange avec VII, F = 141–142,5°.

Déshydrogénation de VIII *en méthyl-1-naphtalène*. Un gramme de l'acide VIII, 0,2 g de palladium sur charbon (10 %) et 5 cm³ de benzène déthiophéné sont chauffés en tube scellé, en atmosphère d'azote, à 350–400° pendant 21 heures. Après filtration du catalyseur on chasse le benzène sous vide et le résidu est distillé en boules. On obtient 0,1 g d'un liquide incolore Eb_{20} = 120°, d'odeur aromatique, donnant un test positif (coloration bleu-vert foncé) avec le chlorure d'aluminium dans le chloroforme.

Picrate. Fait sur la totalité. Recristallisé deux fois dans l'alcool. Aiguilles jaune d'or, F = 136–8°. Mélange avec un échantillon authentique (F = 135–7°): F = 135–137,5°. Littérature[23] F = 141°.

Acide oxo-4-méthyl-1-décahydronaphtalènedicarboxylique-1,2 (XI, R = H). (1) *Forme hydratée*. Huit grammes de produit d'addition sont dissous dans 100 cm³ de

soude aqueuse à 3% par chauffage à 80°; puis on fait bouillir une ½ heure. Après décoloration, on acidifie par l'acide chlorhydrique concentré, refroidit à 0° pendant une heure, et essore le précipité cristallin formé. Rendement 5,2 g (72%) $F = 162$–4° déc. Recristallisé dans le méthanol aqueux. Plaquettes, $F = 163$–165° déc.

Analyse:	$C_{13}H_{18}O_5.H_2O$,	Calc%	C 57,33	H 7,39
	(272)	Tr	57,49	7,51

(2) *Forme anhydre*. Obtenu par extraction à l'éther du précipité qui se forme dans l'hydrolyse précédente. Recristallisé dans l'éther-éther de pétrole. Obtenue également par dissolution de la forme hydratée dans le benzène et évaporation à sec sous vide, l'opération étant répétée plusieurs fois. Cristaux blancs, $F = 167$–169° déc.

Analyse:	$C_{13}H_{18}O_5$,	Calc%	C 61,40	H 7,13
	(254)	Tr	61,45	7,34

Bis-*sel de S-benzylisothiouronium*. $F = 147$–8° (alcool 50%).

Analyse:	$C_{29}H_{38}N_4O_5S_2$,	Calc%	N 9,55
	(554)	Tr	9,87

Anhydride de l'acide oxo-4-méthyl-1-décahydronaphtalène-dicarboxylique-1,2. Par reflux 1 heure de 0,5 g de diacide cétonique (XI, R = H) dans 5 cm³ de chlorure d'acétyle, on obtient après évaporation à sec sous vide et lavage à l'éther de pétrole, 0,4 g d'un solide blanc, $F = 150$–4°. Deux recristallisations dans un peu de benzène donnent des aiguilles blanches, F = 158–159°

Analyse:	$C_{13}H_{16}O_4$,	Calc%	C 66,10	H 6,78
	(236)	Tr	66,37	6,89

Hydrolysé par la soude 3% à 80° en le diacide (XI, R = H).

Anilide-acide. Préparé par la technique décrite plus haut. Rendement quantitatif. Paillettes brillantes, $F = 210$–211° déc. (alcool 75°).

Analyse:	$C_{19}H_{23}NO_4$,	Calc%	C 69,30	H 6,99	N 4,25
	(329)	Tr	68,77	6,75	4,28

Obtenu aussi par saponification (potasse alcoolique 0,2 N à reflux 1/2 heure) de l'anilide correspondant à VII.

Oxo-4-méthyl-1-décahydronaphtalènedicarboxylate de méthyle-1,2(XI, R = CH_3). L'action d'un excès d'une solution éthérée de diazométhane sur une suspension de l'acide dans l'éther, à 0°, conduit à cet ester avec un rendement de 95%. Longues aiguilles prismatiques, $F = 101$–2° (méthanol).

Analyse:	$C_{15}H_{22}O_5$,	Calc%	C 63,82	H 7,80
	(282)	Tr	63,70	7,94

Dinitro-2,4-phénylhydrazone. Paillettes jaune d'or. $F = 212$–213° (benzène-alcool)

Analyse:	$C_{21}H_{26}N_4O_8$,	Calc%	N 12,12
	(462)	Tr	11,84

Anhydride de l'acide cis-*anti*-cis-*méthyl*-1-*décahydronaphtalène-dicarboxylique*-1,2 (IX). Deux grammes de produit d'addition VII en solution dans 10 cm³ d'acide

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acétique glacial sont hydrogénés au contact de 0,3 g de platine Adams sous une pression de 50 kg, à la température ambiante, pendant 6 heures. Après filtration du catalyseur, on concentre sous vide. Il se forme un précipité cristallin qui est essoré, lavé avec un peu d'acide acétique, puis d'éther. $F = 127–129°$. Rendement 1,25 g (78%). Cristallise dans l'éther de pétrole en gros prismes incolores $F = 129,5–131°$.

Analyse:	$C_{12}H_{18}O_3$,	Calc%	C 70,27	H 8,11
	(222)	Tr	70,10	7,80

Anilide-acide. Préparé de la manière habituelle, il cristallise à l'état pur dans le mélange réactionnel. $F = 157–158°$.

Analyse:	$C_{19}H_{25}NO_3$,	Calc%	C 72,38	H 7,93	N 4,44
	(315)	Tr	72,13	7,72	4,60

Acide cis-*anti*-cis-*méthyl*-1-*décahydronaphtalènedicarboxylique*-1,2 (X, R = H). L'anhydride précédent (4,4 g) est hydrolysé par 80 cm³ de soude (3%) à 60–80°. L'acidification à 0° par l'acide chlorhydrique concentré donne 4,5 g d'un solide blanc $F = 168–171°$ déc. Recristallisé deux fois dans l'acétone. Le point de fusion de cet acide peut s'échelonner depuis 175° jusqu'à 182°, selon la température initiale et la vitesse de chauffage. Quand on chauffe rapidement depuis 170°, il fond à 180–182° en se décomposant.

Analyse:	$C_{13}H_{20}O_4$,	Calc%	C 65,00	H 8,33
	(240)	Tr	65,02	8,14

Par chauffage de quelques minutes à 190° et refroidissement, l'acide redonne l'anhydride, $F = 128–130°$, recristallisé dans l'éther de pétrole, $F = 129,5–131°$, qui n'abaisse pas le point de fusion de IX.

Cis-*anti*-cis-*méthyl*-1-*décahydronaphtalènedicarboxylate de méthyle*-1,2 (X, R = CH_3). Trois grammes d'acide en suspension dans 50 cm³ d'éther sont traités à 0°, en agitant, par un excès d'une solution éthérée de diazométhane. Après évaporation sous vide, le résidu est distillé en boules en donnant 3,15 g d'une huile visqueuse incolore $Eb_{0,02} = 125–130°$ qui cristallise par refroidissement. Recristallisé deux fois dans peu d'éther de pétrole. Gros prismes de forme allongée $F = 58–59,5°$.

Analyse:	$C_{15}H_{24}O_4$,	Calc%	C 67,16	H 8,95
	(268)	Tr	67,19	8,78

Acide cis-*anti*-trans-*méthyl*-1-*décahydronaphtalènedicarboxylique*-1,2. Quatre grammes de diester méthylique cis sont ajoutés à une solution de 7 g de sodium dans 225 cm³ de méthanol absolu. On fait refluer pendant 22 heures, puis concentre au quart sous vide. Après addition de 75 cm³ d'eau, on fait encore refluer pendant 4 heures, puis on évapore à sec sous vide, dissous le résidu dans le minimum d'eau et acidifie par l'acide chlorhydrique concentré après décoloration. Rendement 3 g d'un solide blanc, $F = 216–220°$. Deux recristallisations dans un peu d'acétone donnent des aiguilles prismatiques, $F = 224–227°$ déc.

Analyse:	$C_{13}H_{20}O_4$,	Calc%	C 65,00	H 8,33
	(240)	Tr	65,25	8,05

Cis-*anti*-trans-*méthyl*-1-*décahydronaphtalènedicarboxylate de méthyle*-1,2. Obtenu

de la manière habituelle par action du diazométhane dans l'éther sur le diacide correspondant. L'évaporation à sec sous vide donne un huile qui cristallise rapidement. Recristallisé deux fois dans l'éther de pétrole. Prismes incolores. F = 49,5–50,5°.

Analyse:	$C_{15}H_{24}O_4$,	Calc%	C 67,16	H 8,95
	(268)	Tr	67,34	9,02

Anhydride de l'acide cis-*anti*-trans-*méthyl*-1-*décahydronaphtalènedicarboxylique*-1,2. 0,45 g d'acide trans sont traités par 5 cm³ de chlorure d'acétyle au reflux pendant 2,5 heures. Après évaporation sous vide, l'huile résiduelle cristallise rapidement. Le produit est recristallisé dans l'éther de pétrole. Longues aiguilles. F = 89,5–90°.

Analyse:	$C_{13}H_{18}O_3$,	Calc%	C 70,27	H 8,11
	(222)	Tr	70,59	7,94

Anilide acide. Méthode de préparation habituelle. Précipite à l'état pur du mélange réactionnel. Petites aiguilles. F = 219–221° déc.

Analyse:	$C_{19}H_{25}NO_3$,	Calc%	C 72,38	H 7,93	N 4,44
	(315)	Tr	72,40	7,75	4,76

Acide trans-*anti*-cis-*méthyl*-1-*décahydronaphtalènedicarboxylique*-1,2 (XII, R = H). (1) 2,54 g de diacide cétonique (XI, R = H) en solution 50 cm³ de toluène et 20 cm³ d'acide acétique sont ajoutés à 30 g de zinc amalgamé, 20 cm³ d'eau et 50 cm³ d'acide chlorhydrique concentré. On fait refluer pendant 31 heures, au cours desquelles sont rajoutées 5 portions de 20 cm³ d'acide chlorhydrique concentré. Après le traitement habituel, on obtient 2,3 g d'une huile jaune très visqueuse qui cristallise en partie par addition d'un peu d'éther de pétrole. Rdt = 1,6 g (66,7%). F = 173–5° déc. Recristallisé deux fois dans l'acétone. Petits cristaux, F = 177–8° déc.

Analyse:	$C_{13}H_{20}O_4$,	Calc%	C 65,00	H 8,33
	(240)	Tr	65,17	7,96

Point de fusion mélangé avec X, R = H: 149–153° déc.

(2) 2 g d'acide cétonique, 2 g de potasse, 1 cm³ hydrate d'hydrazine et 15 cm³ de triéthylène glycol sont chauffés de façon à distiller 4 à 5 cm³ très lentement, après quoi on porte à reflux pendant 3 heures. Après refroidissement, on étend avec un volume d'eau et verse doucement dans 9 cm³ d'acide chlorhydrique 6 N en refroidissant. L'huile qui précipite est extraite à l'éther et les solution éthérées lavées à l'eau, puis épuisées à la soude 30%. Les liqueurs alcalines décolorées et concentrées sont acidifiées et l'acide est extrait à l'éther. Le résidu de l'évaporation de l'éther est dissous dans le minimum de ce solvant à chaud et refroidi. Il précipite 0,4 g (Rdt 21%) de plaquettes. F = 175–7°. Recristallisé dans l'acétone. F = 176,5–178° déc. Mélange avec le précédent, F = 176,5–177,5° déc.

Anhydride de l'acide trans-*anti*-cis-*méthyl*-1-*décahydronaphtalènedicarboxylique*-1,2. On fait refluer pendant 3 heures une solution de 0,5 g de l'acide précédent dans 5 cm³ de chlorure d'acétyle. Après évaporation à sec sous vide, on distille deux fois en boules pour obtenir 0,4 g d'un liquide incolore visqueux $Eb_{0,005}$ = 125–130°, que

nous n'avons pas pu faire cristalliser.

Analyse:	$C_{13}H_{18}O_3$.	Calc%	C 70,27	H 8,10
	(222)	Tr	70,16	7,42

Anilide-acide. Préparé de la manière habituelle. Rendement quantitatif. Paillettes brillantes. $F = 232$–$234°$ déc. (alcool)

Analyse:	$C_{19}H_{25}NO_3$.	Calc%	C 72,38	H 7,93	N 4,44
	(315)	Tr	72,26	7,76	4,81

Trans-*anti*-cis-*décahydronaphtalènedicarboxylate de méthyle*-1,2. Obtenu avec un rendement de 83% par action d'un excès d'une solution éthérée de diazométhane sur une suspension de l'acide dans l'éther, à 0°, et distillation en boules. $Eb_{0,01} = 120°$. Cristallise lentement par abandon à la température ambiante. Recristallisé deux fois dans un peu d'éther de pétrole. Gros prismes $F = 60{,}5$–$62°$. Mélange avec XII, $R = CH_3$: $F = 37$–$45°$.

Analyse:	$C_{15}H_{24}O_4$.	Calc%	C 67,16	H 8,95
	(268)	Tr	67,31	8,61

Acide trans-*anti*-cis-*méthyl*-1-*carbométhoxy*-2-*décahydronaphtalènecarboxylique*-1. L'ester ci-dessus (1,35 g) est saponifié par de la soude à 40% (20 cm³) à reflux 3,5 heures, ou par de la potasse méthanolique à 30% à reflux 5 heures. Dans les deux cas, l'acidification de la solution aqueuse alcaline donne une huile qui est extraite à l'éther. Le résidu de l'évaporation de l'éther cristallise au contact de l'éther de pétrole. Les cristaux sont essorés et lavés à l'éther de pétrole. Rdt. 0,95 g (75%). La recristallisation dans un peu d'éther de pétrole fournit de petites aiguilles, $F = 99$–$100°$.

Analyse:	$C_{14}H_{22}O_4$.	Calc%	C 66,14	H 8,66
	(254)	Tr	66,66	8,94

Equivalent de neutralisation. 0,5 g de produit en solution méthanolique sont neutralisés par 21,2 cm³ de soude 0,09 N en présence de phénolphtaléine. Tr = 261. Calc. (diacide) = 120. Calc. (hémi-ester) = 254.

Par action d'une solution éthérée de diazométhane, on obtient le diester de départ, $F = 60$, 5–62° (point de fusion mélangé non abaissé).

Tentative d'isomérisation du trans-*anti*-cis-*décahydronaphtalènedicarboxylate de méthyle*-1,2 *par le méthylate de sodium*. 1,3 g de diester sont ajoutés à une solution de 2,25 g de sodium dans 75 cm³ de méthanol absolu. Après un reflux de 22 heures, on traite selon le mode opératoire décrit plus haut. Les produits acides sont extraits à l'éther et l'évaporation donne 1 g d'un produit pâteux jaune clair qui ne veut pas cristalliser. 0,9 g de ce produit en solution méthanolique sont neutralisés par 20,8 cm³ de soude 0,17 N. Calculé pour l'hémi-ester: 20,6 cm³. Calculé pour le diacide: 44,1 cm³. Par action d'une solution éthérée de diazométhane, on revient au diester initial, $F = 60$–2° (mélange, $F = 60$–61,5°).

Saponification énergique du trans-*anti*-cis-*méthyl*-1-*décahydronaphtalènedicarboxylate de méthyle*-1,2. 0,45 g de diester sont placés dans un tube scellé avec 1,5 g de potasse en solution dans 2 cm³ d'eau et 2 cm³ d'alcool 95°. On chauffe à 140° pendant 18 heures. Après le traitement habituel, le solide obtenu est dissous dans l'acétone et

décoloré. La solution acétonique concentrée et refroidie laisse déposer 0,25 g de cristaux prismatiques $F = 161$–$166°$ déc. (mélange avec le diacide *cis*, $F = 167$–$170°$ déc.). Par évaporation à sec des eaux-mères, on obtient des cristaux, $F = 165$–$168°$ déc (0,1 g). Ce produit est donc vraisemblablement constitué d'un mélange des acides *cis* et *trans*.

Tentative d'isomération de XI, R = H *par la soude*. On fait refluer pendant une nuit une solution de 0,4 g de diacide cétonique dans 10 cm³ de soude à 20%. Après acidification et extraction à l'éther, on obtient 0,4 g d'un solide, $F = 166$–$168°$ déc. qui recristallise dans l'éther-éther de pétrole. $F = 167$–$9°$ déc. N'abaisse pas le point de fusion de l'acide initial. Avec le diazométhane dans l'éther on obtient le diester méthylique, $F = 98$–$100°$ (brut). Le mélange avec XI, R = CH_3 fond à 100–102°. Dinitro-2,4-phénylhydrazone de l'ester: paillettes jaune d'or, $F = 213$–$4°$. N'abaisse pas le point de fusion de la dinitro-2,4-phénylhydrazone de XI, R = CH_3.

Essais d'isomérisation dans les conditions du Clemmensen. (1) 0,5 g de IX sont traités par 10 cm³ d'acide chlorhydrique aux 2/3, 1 cm³ d'acide acétique et 5 cm³ de toluène, à reflux pendant 40 heures. On obtient, après le traitement habituel, 0,5 g d'un solide $F = 125$–$128°$. Recristallisé dans l'éther de pétrole, $F = 129$–$131°$, non abaissé en mélange avec le produit initial. Hydrolysé par la soude 1 N à 60–80° en le diacide $F = 180$–$182°$ déc. (2) 0,5 g d'acide X, R = H sont traités de la même façon. On obtient un solide F = 124–8°. Recristallisé dans l'éther de pétrole, $F = 129{,}5$–$131°$. N'abaisse pas le point de fusion d'un échantillon de IX. Hydrolysé par la soude 1 N à 60–80° en le diacide initial.

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A SYNTHESIS OF 6:8–DIHYDROXYFLAVONE

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Abstract—Work on routes to the synthesis of 6:8-dihydroxyflavone, one of which proved successful, is described.

6:8-Dihydroxyflavone which, until recently, was the only unknown of the six possible dihydroxyflavones unsubstituted in the 2-phenyl group, has proved unexpectedly difficult to synthesise.[1] We have explored a number of routes and have now obtained 6:8-dimethoxyflavone in 4 per cent yield by a Mentzer reaction[2] involving the thermal condensation of 2:4-dimethoxyphenol with ethyl benzoylacetate.[3] Simpson[4] synthesised 6:8-dihydroxyflavone shortly before the above work was completed and courteously agreed to simultaneous publication of preliminary notes.[3,4] Demethylation of the dimethoxyflavone required prolonged treatment with hydriodic acid. Thermal condensation of resorcinol with ethyl 3-oxo-2-phenylpropionate gave 7-hydroxy-3-phenylcoumarin and not 7-hydroxy*iso*flavone.[5]

8-Amino-6-methoxyflavone was also synthesised but it was not found possible to replace the amino by the hydroxyl group. 6-Methoxyflavone was readily produced by treatment of 6-methoxy-5-*p*-tolylsulphonyloxyflavone with hydrogen in presence of Raney nickel,[6] but the method failed with 6:8-dimethoxy-5-*p*-tolylsulphonyloxyflavone. Other unsuccessful approaches are mentioned in the experimental section.

Rajagopalan, Seshadri, and Varadarajan's synthesis[7] of 5:6:8-trihydroxyflavone includes the interaction of 5-hydroxy-8-methoxyflavone with hexamine to give 6-formyl-5-hydroxy-8-methoxyflavone. We obtained mainly di-(5-hydroxy-8-methoxyflavon-6-yl)methane from this reaction, and found it preferable to hydroxylate (Elbs persulphate method) 5-hydroxy-6-methoxyflavone in the 8-position.

EXPERIMENTAL

Crystallisation was from ethanol unless otherwise stated.

6:8-*Dihydroxyflavone*

2:4-Dimethoxyphenol[8] (10 g) was heated under an air condenser at 270° for 8 hr with ethyl benzoylacetate[9] (15 g). A current of nitrogen was used to remove ethanol and water as formed. The residue was extracted with ether and the ethereal solution

[1] W. Baker, N. C. Brown and J. A. Scott *J. Chem. Soc.* 1922 (1939).
[2] C. Mentzer, D. Molho and P. Vercier *C.R. Acad. Sci., Paris* **232**, 1488 (1951); D. Pillon, *Bull. Soc. Chim. Fr.* 39 (1955).
[3] J. E. Gowan, S. P. MacGiolla Riogh, G. J. MacMahon, B. R. O'Farrell, S. Ó'Cléirigh, E. M. Philbin and T. S. Wheeler *Chem. and Ind. (Rev.)* 1672 (1955).
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[6] G. W. Kenner and M. A. Murray *J. Chem. Soc.* S178 (1949).
[7] S. Rajagopalan, T. R. Seshadri and S. Varadarajan *Proc. Indian Acad. Sci.* A**31**, 31 (1950).
[8] E. Späth, M. Pailer and G. Gergely *Chemie.* **73**, 935 (1940).
[9] R. L. Shriner, A. G. Schmidt and L. J. Roll *Org. Synth. Coll.* **2**, 266 (1943).

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was washed with dilute alkali (solution A—see below) and with water. Removal of the solvent gave an oil which was chromatographed on alumina. The chromatogram was developed with light petroleum (b.p. 40–60°). Five bands were observed in ultra-violet light. The first four were eluted with light petroleum and the fifth, which proved to be 6:8-*dimethoxyflavone*, with benzene-petroleum ether (30 : 70). This compound separated from ligroin in needles (0·5 g), m.p. 148–149° and 152–153° (dimorphic) (Found: C, 72·6; H, 5·0; OMe, 22·4. $C_{17}H_{14}O_4$ requires C, 72·3; H, 5·0; 2OMe, 22·0 per cent). Dr. T. H. Simpson (personal communication) states that the m.p. was not depressed by addition of 6:8-dimethoxyflavone synthesised by him from the corresponding chalkone.[4]

Demethylation by hydriodic acid–acetic anhydride under reflux for 4 hr gave 6:8-*dihydroxyflavone*, which crystallised from aqueous ethanol in yellow needles, m.p. 274° (decomp.) (Found: C, 71·2; H, 4·1. $C_{15}H_{10}O_4$ requires C, 70·9; H, 4·0 per cent). 6:8-*Diacetoxyflavone* formed needles, m.p. 196–197° (Found: C, 67·0; H, 4·2. $C_{19}H_{14}O_6$ requires C, 67·4; H, 4·2 per cent). Each of the three flavones in sulphuric acid solution exhibited a yellow fluorescence in ultra-violet light.

Acidification of the alkaline solution A (above) gave 3-benzoyl-3:4-dihydro-2:4-di-oxo-6-phenyl-2*H*-pyran, m.p. and mixed m.p. with an authentic sample prepared by refluxing ethyl benzoylacetate,[10] 170–172°.

Wavelengths for maximum light absorption in ethanolic solution (λ_{max} in mμ) are shown below for some 6- and 8-substituted flavones: 6-hydroxyflavone (271,303); 8-hydroxyflavone (267); 6:8-dihydroxyflavone (276); 6-methoxyflavone (267,302); 8-methoxyflavone (265); 6:8-dimethoxyflavone (275); 6-acetoxyflavone (255,296); 8-acetoxyflavone (254,295); 6:8-diacetoxyflavone (257,297).

7-Hydroxy-3-phenylcoumarin

Resorcinol (15 g) was heated with ethyl 3-oxo-2-phenylpropionate (15 g) in nitrogen at 270–280° until evolution of water and ethanol ceased (15 min). The product was refluxed with acetone (1·5 l), dimethyl sulphate (20 g), and potassium carbonate (200 g) for 6 hr, solids were removed, and the filtrate diluted with water (2 l). The ethereal solution of the resulting precipitate was washed with alkali. The residue after removal of the solvent was chromatographed on alumina. The fourth band which was visible in ultra-violet light, was eluted by light petroleum and yielded 7-methoxy-3-phenylcoumarin, which crystallised in prisms (0·7 g), m.p. 124° (Found: C, 76·5; H, 4·7; OMe, 12·2. Calc. for $C_{16}H_{12}O_3$: C, 76·2; H, 4·8; OMe, 12·3 per cent). Demethylation by hydriodic acid in acetic anhydride gave 7-hydroxy-3-phenylcoumarin which separated from aqueous ethanol in prisms, m.p. 207°. Baker[5] gives m.p. 124° for the methoxycoumarin and m.p. 207–208° for the hydroxycoumarin.

Numerous unsuccessful attempts[11] were made to apply Ruhemann's flavone synthesis[12] to the preparation of 6:8-dihydroxyflavone. This synthesis involves cyclisation of 3-aryloxycinnamoyl halides prepared from the adducts of phenols to 3-arylpropiolic esters.

Methyl 2-hydroxy-3:5-dimethoxybenzoate

A mixture of 2:3:5-trimethoxybenzoic acid,[1] acetic anhydride, and hydriodic acid

[10] A. Baeyer and W. H. Perkin *Chemie.* **17**, 64 (1884).
[11] B. R. O'Farrell M.Sc. Thesis, National University of Ireland (1956).
[12] S. Ruhemann *Chemie.* **46**, 2188 (1913); **54**, 912 (1921).

was heated at 60° for 12 hr, and the product was added to aqueous sodium hydrogen sulphite. The precipitated *2-hydroxy-3:5-dimethoxybenzoic acid* separated from water in needles, m.p. 183° (Found: C, 54·4; H, 4·9; OMe, 31·5. $C_9H_{10}O_5$ requires C, 54·5; H, 5·1; 2OMe, 31·3 per cent), which gave a blue colour with ethanolic ferric chloride. The *methyl ester* (Fischer-Speier) crystallised from water in needles, m.p. 92° (Found: C, 56·4; H, 5·7; OMe, 43·3. $C_{10}H_{12}O_5$ requires C, 56·6; H, 5·7; 3OMe, 43·8 per cent), which exhibited a green ethanolic ferric colour. The positive ethanolic ferric reactions of the acid and ester confirmed that, as expected, demethylation had occurred *ortho* to the carbonyl group. No useful result was obtained in attempts to prepare benzoyl-2-hydroxy-3:5-dimethoxybenzoylmethane (the hydroxydiketone corresponding to 6:8-dimethoxyflavone) by a Claisen condensation of this ester with acetophenone using sodium in dry xylene.

8-Amino-6-methoxyflavone

A mixture of 2-hydroxy-5-methoxyacetophenone[1] (10 g), acetic acid (120 ml), and acetic anhydride (9 ml) was cooled to solidification and treated with nitric acid (3·0 ml; *d* 1·5); after 1 hr the liquid-solid product was added to ice.

2-Hydroxy-5-methoxy-3-nitroacetophenone, which separated, crystallised from methanol in yellow plates (7·2 g), m.p. 112° (Found: C, 50·9; H, 4·2; N, 6·7. $C_9H_9O_5N$ requires C, 51·2; H, 4·3; N, 6·6 per cent). This ketone was oriented by hypobromite oxidation.[13] The product did not depress the m.p. of an authentic sample of 2-hydroxy-5-methoxy-3-nitrobenzoic acid.[14]

No useful result was obtained in attempts to nitrate 2:5-diacetoxyacetophenone or 2:5-dimethoxyacetophenone. The *2:4-dinitrophenylhydrazone* of this latter ketone formed red needles, m.p. 170° (Found: C, 53·7; H, 4·5; N, 16·1; OMe, 17·1. $C_{16}H_{16}O_6N_4$ requires C, 53·3; H, 4·5; N, 15·6; 2OMe, 17·2 per cent).

Methylation of 2-hydroxy-5-methoxy-3-nitroacetophenone (methyl sulphate-potassium carbonate-acetone) gave *2:5-dimethoxy-3-nitroacetophenone* which crystallised in plates, m.p. 52–53° (Found: C, 53·6; H, 4·9; N, 5·9; OMe, 28·2. $C_{10}H_{11}O_5N$ requires C, 53·3; H, 4·9; N, 6·2; 2OMe, 27·6 per cent).

2-Benzoyloxy-5-methoxy-3-nitroacetophenone which was prepared by the action of pyridine and benzoyl chloride on 2-hydroxy-5-methoxy-3-nitroacetophenone formed plates, m.p. 105–106° (Found: C, 61·0; H, 4·2; N, 4·6; OMe, 9·8. $C_{16}H_{13}O_6N$ requires C, 61·0; H, 4·2; N, 4·4; OMe, 9·8 per cent). A mixture of this ester (15 g), potassium hydroxide (3 g), and pyridine (60 ml) was shaken for 72 hr and the product was added to ice and hydrochloric acid. The precipitate of *benzoyl-2-hydroxy-5-methoxy-3-nitrobenzoylmethane* crystallised in red needles (4·5 g), m.p. 124° (Found: C, 60·6; H, 4·3; N, 4·6; OMe, 9·9. Required: as for the ester). The ethanolic ferric colour was red.

A solution of the diketone in acetic acid containing a trace of hydrochloric acid was boiled for 45 min, and then diluted with water. *6-Methoxy-8-nitroflavone* which separated, formed needles, m.p. 196–197° from acetic acid (Found: C, 64·3; H, 4·0; N, 4·8; OMe, 9·7. $C_{16}H_{11}O_5N$ requires C, 64·6; H, 3·7; N, 4·7; OMe, 10·4 per cent). Reduction by stannous chloride in hydrochloric acid yielded *8-amino-6-methoxyflavone* which crystallised in yellow needles, m.p. 204–205° (Found: C, 71·9; H, 5·1;

[13] W. S. Johnson, C. D. Gutsche and R. D. Offenhauer *J. Amer. Chem. Soc.* **68**, 1648 (1946).
[14] A. Klemenc *Mh. Chem.* **33**, 1243 (1912).

N, 5·2; OMe, 12·3. $C_{16}H_{13}O_3N$ requires C, 71·9; H, 4·9; N, 5·2; OMe, 11·6 per cent). 8-*Acetamido-6-methoxyflavone* separated from methanol in needles, m.p. 254–256° (Found: C, 70·0; H, 5·1; N, 4·5; OMe, 10·2. $C_{18}H_{15}O_4N$ requires C, 69·9; H, 4·9; N, 4·5; OMe, 10·0 per cent). The aminoflavone when refluxed with picryl chloride in ethanol for 15 min gave 6-*methoxy-8-picrylaminoflavone* which formed orange needles, m.p. 236–238° (Found: C, 55·2; H, 3·1; N, 11·6; OMe, 6·8. $C_{22}H_{14}O_4N_4$ requires C, 55·2; H, 3·0; N, 11·7; OMe, 6·5 per cent).

Many unsuccessful attempts were made by diazotisation and subsequent hydrolysis to convert 8-amino-6-methoxyflavone into 8-hydroxy-6-methoxyflavone.[15,16] Other experiments involved efforts at direct replacement of the amino group by hydroxyl by treatment with acid.[16,17] An endeavour was also made to convert 8-acetamido-6-methoxyflavone into the 8-hydroxy compound by the action of alkali.[18] 6-Methoxy-8-picrylaminoflavone was also resistant to acid and alkaline hydrolysis. No success was obtained in essays to apply a Bucherer-type reaction to the aminoflavone.

Di-(5-hydroxy-8-methoxyflavon-6-yl)methane

A mixture of 5-hydroxy-8-methoxyflavone (0·6 g),[7] acetic acid (20 ml), and hexamine (2·0 g) was heated at 100° for 6 hr, and hydrochloric acid (20 ml; 1 : 1) was added. Heating was continued for 1 hr and the product was diluted with water. The precipitated *diflavonylmethane* separated from benzene in yellow needles (0·15 g), m.p. 299–300° (Found: C, 72·6; H, 4·6. $C_{33}H_{24}O_8$ requires C, 73·3; H, 4·4 per cent). The ethanolic ferric colour was green. The *di-acetate* formed microcrystals from nitrobenzene, m.p. 318–322° (Found: C, 70·1; H, 4·7. $C_{37}H_{28}O_{10}$ requires C, 70·3; H, 4·5 per cent).

5:6:8-*Trihydroxyflavone*

Aqueous potassium persulphate (1·7 g in 50 ml water) was added at 15–20° during 2 hr to a stirred suspension of 5-hydroxy-6-methoxyflavone[19] (1 g) in water (20 ml) containing potassium hydroxide (1.2 g) and pyridine (30 ml). After 48 hr the solution was acidified to congo red and unchanged hydroxymethoxyflavone removed. The filtrate was heated with sodium sulphite (3 g) and hydrochloric acid (30 ml) at 100° for 1 hr. It then yielded to ether crude 5:8-dihydroxy-6-methoxyflavone which was crystallised from methanol. The crystals (0·07 g) when refluxed with hydroidic acid and acetic acid for 2 hr gave 5:6:8-trihydroxyflavone, m.p. 237–239° (acetate, m.p. 217–218°). Rajagopalan, Seshadri, and Varadarajan[7] give m.p. 236–237° and 214°. Acetylation of the crude 5:8-dihydroxy-6-methoxyflavone yielded 5:8-*diacetoxy-6-methoxyflavone* which crystallised from methanol in needles, m.p. 199–201° (Found: C, 64·9; H, 4·3. $C_{20}H_{16}O_7$ requires C, 65·2; H, 4·4 per cent). This acetate when treated with ethanolic hydrochloric acid at 100° for 30 min gave 5:8-*dihydroxy-6-methoxyflavone* which crystallised from aqueous ethanol in reddish needles, m.p. 254° (decomp.) (Found: C, 68·0; H, 4·5; OMe, 10·8. $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·3; OMe, 10·9 per cent). A mixture of the dihydroxymethoxyflavone (0·2 g)

[15] N. Anand and K. Venkataraman *Proc. Indian Acad. Sci.* **A26**, 279 (1947); Bräunlich "Beilstein" **6**, 769 (1923); Ad. Claus and R. Wallbaum *J. Prakt. Chem.* **56**, 48 (1897); A. Hantzsch and E. Jochem *Chemie.* **34**, 3337 (1901); H. H. Hodgson and J. Walker *J. Chem. Soc.* 1620 (1933); Woodward *Org. Synth.* **25**, 55 (1945).

[16] R. N. Iyer and K. Venkataraman *Proc. Indian Acad. Sci.* **A37**, 629 (1953).

[17] C. Graebe *Chemie.* **16**, 862 (1883); E. Späth and E. Dobrovolny *Ibid.* **71**, 1831 (1938).

[18] W. W. Hartman, J. R. Byers and J. B. Dickey *Org. Synth. Coll.* **2**, 451 (1943).

[19] W. Baker *J. Chem. Soc.* 956 (1939).

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ethanol (40 ml), water (16 ml), potassium carbonate (2 g) and dimethyl sulphate (1 ml) was shaken for 30 min[20] and the product was diluted with water. The precipitate of 5-*hydroxy*-6:8-*dimethoxyflavone* separated from methanol in light brown needles (0·12 g), m.p. 183–184° (Found: C, 68·2; H, 5·1; OMe, 20·7. $C_{17}H_{14}O_5$ requires C, 68·5; H, 4·7; 2OMe, 20·8 per cent).

5-Hydroxy-6-methoxyflavone on treatment with *p*-toluenesulphonyl chloride, acetone, and potassium carbonate yielded 6-*methoxy*-5-p-*tolylsulphonyloxyflavone*, m.p. 204–206° (from acetone) (Found: C, 65·4; H, 4·4; S, 7·5. $C_{23}H_{18}O_6S$ requires C, 65·4; H, 4·3; S, 7·6 per cent). Reduction of the sulphonyloxyflavone by the hydrogen-Raney nickel method[6] gave 6-methoxyflavone (mixed m.p. confirmation). 6:8-*Dimethoxy*-5-p-*tolylsulphonyloxyflavone* crystallised from acetic acid in aggregates, m.p. 246–247° (Found: C, 64·1; H, 4·7; S, 7·5. $C_{24}H_{20}O_7S$ requires C, 63·7; H, 4·5; S, 7·1 per cent). Attempts to obtain 6:8-dimethoxyflavone by hydrogenolysis of the above compound in the presence of Raney nickel were unsuccessful.

α- and β-4-Hydroxyflavan

Hydrogen was passed during 2 hr through an ethanolic solution (500 ml) of 5-*p*-tolylsulphonyloxyflavone (1 g) containing Raney nickel (6 g). Solids were removed and the filtrate was concentrated to 20 ml. The precipitate formed on addition of water gave a trace of α-4-hydroxyflavan (soluble in hot water) which formed needles, m.p. 119–120° (Found: C, 79·8; H, 6·4. Calc. for $C_{15}H_{14}O_2$: C, 79·6; H, 6·2 per cent) (acetate, m.p. 84–85°). Freudenberg and Orthner[21] give m.p. 119° and 85–86°. The water-insoluble fraction (*β*-4-hydroxyflavan) separated from ligroin in needles, m.p. 143–144° (Found: C, 79·1; H, 6·4. Calc. as above) (acetate, m.p. 98°). Karrer, Yen, and Reichstein[22] give m.p. 148–149° and 97–98°. Gupta, Jain, and Seshadri[23] obtained only the *β*-compound from 5- and 7-*p*-tolylsulphonyloxyflavone.

No satisfactory result was obtained in attempts to remove the sulphonyloxy group from 6-methoxy-5-*p*-tolylsulphonyloxyflavone by Clar's method (zinc dust, sodium chloride, zinc chloride)[24] or by the use of lithium aluminium hydride.[25]

Diethyl flavon-7-yl phosphate

A mixture of tetra-ethylpyrophosphate (6 ml), 7-hydroxyflavone (2·5 g), and N-sodium hydroxide (10 ml) was shaken for 2 hr, diluted with water, and extracted with ether. The ethereal solution was washed successively with dilute alkali, acid, and water. Removal of the solvent gave *diethyl flavon-7-yl phosphate* which formed plates, m.p. 60–61° (0·7 g) from light petroleum (b.p. 40–60°) (Found: C, 60·6; H, 5·2; P, 8·1. $C_{19}H_{19}O_6P$ requires C, 61·0; H, 5·1; P, 8·3 per cent). This compound was not altered by treatment with sodium in liquid ammonia.[26]

7-*Chloroflavone*

7-Hydroxyflavone (1 g) was heated with phosphorus oxychloride (4 g) until

[20] J. M. Guider, T. H. Simpson and D. B. Thomas *J. Chem. Soc.* 170 (1955).
[21] K. Freudenberg and L. Orthner *Chemie.* **55,** 1748 (1922).
[22] P. Karrer, Y. Yen and I. Reichstein *Helv. Chim. Acta* **13,** 1308 (1930).
[23] V. N. Gupta, A. C. Jain and T. R. Seshadri *Proc. Indian Acad. Sci.* **A38,** 470 (1953); R. Mozingo and H. Adkins *J. Amer. Chem. Soc.* **60,** 669 (1938).
[24] E. Clar *Chemie.* **72,** 1645 (1939); H. W. D. Stubbs and S. H. Tucker *J. Chem. Soc.* 2939 (1951).
[25] P. Karrer and H. Schmid + *Helv. Chim. Acta* **32,** 1371 (1949); C. W. Shoppee and D. D. Evans *J. Chem. Soc.* 540 (1953).
[26] G. W. Kenner and N. R. Williams *J. Chem. Soc.* 522 (1955).

hydrogen chloride was no longer evolved (3 hr), and the product was extracted with hot water. The residual 7-chloroflavone separated from methanol (charcoal) in aggregates (0·8 g), m.p. 155–157° (Found: C, 70·6; H, 3·5: Cl, 14·2. Calc. for $C_{15}H_9O_2Cl$: C, 70·2; H, 3·5; Cl, 13·8 per cent). Cramer and Elschnig[27] give m.p. 158°. 7-*Chloroflavone hydrazone* crystallised from aqueous ethanol in needles, m.p. 178–180°. (Found: C, 65·8; H, 4·0; N, 10·4. $C_{15}H_{11}ON_2Cl$ requires C, 66·5; H, 4·1; N, 10·2 per cent.)

7-Bromoflavone

7-Hydroxyflavone (5 g) was fused with phosphorus pentabromide (13 g) and sodium chloride (1 g) for 1 hr, and the product was extracted with hot water. The residue separated from methanol in micro-crystals (0·4 g), m.p. 157–158° (Found: C, 59·8; H, 3·2. Calc. for $C_{15}H_9O_2Br$: C, 59·8; H, 3·0 per cent). Chen and Chang[28] give m.p. 162–163° for 7-bromoflavone.

Experiments on the replacement of halogen by hydrogen in 7-halogenoflavones were discontinued on the synthesis of 6:8-dimethoxyflavone. These experiments involved the conversion of the halogenoflavone, through the lithium derivative, into the corresponding carboxylic acid.

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[27] F. Cramer and G. H. Elschnig *Chemie*. **89,** 10 (1956).
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THEORY OF ELECTRONIC SPECTRA OF ORGANIC MOLECULES

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Abstract—A theory of the electronic spectra of organic molecules is outlined. The wave-mechanical resonance characteristic for the excited states of polyelectronic systems involves a fluctuation of the transition energy and, in this sense, represents a physical phenomenon which is absent in ground states. An analysis of the electronic perturbations resulting from resonance offers a qualitative, but very detailed, understanding of the observations and conclusions summarised in the author's classification of electronic spectra, if molecular structures are considered to be built up of localised bonds only. The electronic transitions responsible for *R*-, *K*-, and Benzenoid-bands and the effect of terminal groups and of substituents of absorbing systems on the positions of these bands are interpreted.

1. INTRODUCTION

THE present paper outlines a general theory of the electronic spectra of organic molecules. Earlier investigations have established an empirical classification of the absorption bands (*R*-, *K*-, Benzenoid-bands) appearing above 2000 Å and the rules of their behaviour.[1–6]

The author realised that the interpretation of molecular structures with the help of the concept of non-localised bonds (resonance among several idealised valence-bond structures, many-centred molecular orbitals) and of mesomeric or electromeric electron displacements is unable to account for numerous observations and aspects of electronic spectra.[5–7*] This dilemma led to a detailed analysis of other physical and chemical properties of organic compounds which resulted in a confirmation of the conclusions derived from the study of electronic spectra. It could be shown that a consideration of the electronic repulsions, which were previously neglected because they offer considerable difficulties to a mathematical analysis or to a qualitative formal representation, allows a consistent qualitative interpretation of the properties of organic molecules in terms of classical (not idealised) structures and inductive electron displacements only.[8–12] These repulsions also account for the absence of orbital delocalisations.

The foundation for a theoretical analysis of the electronic spectra of polyelectronic

[1] A. Burawoy *Ber. Dtsch. Chem. Ges.* **63**, 3155 (1930); **64**, 464, 1635 (1931); **65**, 941 (1932); *J. Chem. Soc.* 1865 (1937); 1177 (1939); 20 (1941).
[2] A. Gillam and E. S. Stern *Electronic Absorption Spectroscopy in Organic Chemistry* pp. 111. Edward Arnold, London (1954).
[3] A. Burawoy *Disc. Faraday Soc.* **9**, 70, 73 (1950).
[4] A. Burawoy *J. Soc. Dyers and Colourists* **15**, 616 (1949).
[5] A. Burawoy and E. Spinner *J. Chem. Soc.* 2085, 2557 (1955).
[6] A. Burawoy and A. R. Thompson *J. Chem. Soc.* 4314 (1956).
[7] A. Burawoy *Chem. and Ind.* **59**, 855 (1940).
[8] A. Burawoy *Trans. Faraday Soc.* **40**, 537 (1944); *Disc. Faraday Soc.* **10**, 104 (1951); *Chem. Ind.* (*Rec*). **63**, 434 (1944).
[9] A. Burawoy *Contribution to the Study of Molecular Structure* p. 73. Desoer, Liège (1947–1948).
[10] A. Burawoy and J. T. Chamberlain *J. Chem. Soc.* 2310 (1952).
[11] A. Burawoy and E. Spinner *J. Chem. Soc.* 3752 (1954).
[12] J. E. Lennard-Jones and J. A. Pople *Disc. Faraday Soc.* **10**, 9 (1951); J. A. Pople, Quart. Reviews **XI**, 273 (1957).

* Numerous additional examples will be given in subsequent publications.

systems has been laid by Heisenberg[13] who, in introducing the conception of wave-mechanical resonance, not only explained the fact that the simplest polyelectronic entity, the helium atom, forms two independent systems of energy levels, but also gave a wave-mechanical interpretation of electronic perturbation in an *excited* state. Moreover, this concept offered the explanation for the apparent paradox that in polyelectronic systems many electrons appear to participate in the transition, although (generally) only one electron can be excited.

As a result of the interaction (due to electronic repulsions) of its two valency electrons a and b, one of which is excited, the helium atom can exist in two types of excited states corresponding to the symmetrical and antisymmetrical wave-functions I and II respectively. The singlet, identified with I, is less stable, the triplet state, identified with II, which in absorption is already forbidden by spin requirements, is more stable than the interacting fictitious unperturbed excited states of the system corresponding to $\psi_1(a).\psi_2(b)$ and $\psi_1(b).\psi_2(a)$ respectively.

$$\text{I} \qquad \Psi_S = \frac{1}{\sqrt{2}}[\psi_1(a).\psi_2(b) + \psi_1(b).\psi_2(a)]$$

$$\text{II} \qquad \Psi_A = \frac{1}{\sqrt{2}}[\psi_1(a).\psi_2(b) - \psi_1(b).\psi_2(a)]$$

The theoretical developments of the past 25 years have been governed by the aim to systematise qualitatively or to account quantitatively for molecular states in terms of atomic orbitals. The complexity of polyatomic molecules and mathematical limitations necessitated the introduction of numerous simplifying conceptions (e.g. (i) the distinction between the two bonds (σ, π) in the ethylene double bond, (ii) the concept of non-localised bonds, (iii) the attempt to build up electronic structures of molecules with the help of many-centred (as distinct from two-centred) molecular orbitals by analogy to the building-up principle in atomic structures, (iv) the consideration of π electrons only). Unfortunately, these concepts became widely accepted as representing a true physical picture of molecular states. It is the author's contention that these simplifying assumptions are unsuitable or unable to offer a basis for a detailed understanding of the experimental observations related to the electronic spectra of the more complicated organic molecules.

In contrast, the present analysis will be based on the bond orbitals present in covalent linkages, no reduction to atomic orbitals being attempted. It aims at an interpretation of the electronic transitions responsible for the *R*-, *K*- and Benzenoid-bands and of the changes in the transition energies resulting from structural modifications (constitutive changes or replacements of covalent linkages). This analysis, being in the first instance only a qualitative one and, thus, independent of mathematical limitations, does not require any structural simplifications and will be strictly based on and governed by classified experimental data. It will be shown that, on this basis, a consistent consideration of the electronic perturbations in the excited states due to Heisenberg resonance offers a qualitative, but very detailed understanding of the electronic spectra of organic molecules, if the latter are accepted as being built up of localised bonds only.

In view of the increasing complexity of the systems to be discussed, no further use of wave-mechanical formulation will be made, which problem should be left to more

[13] W. Heisenberg *Z. Physik* **38**, 411; **39**, 499 (1926); **41**, 239 (1927).

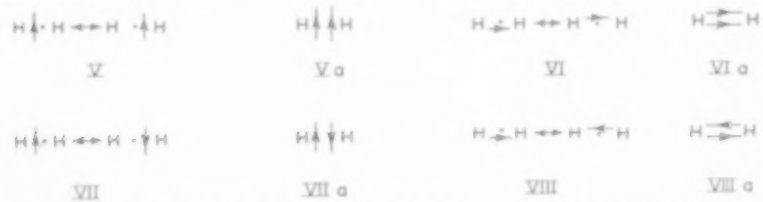
competent theoretical physicists. However, it will be convenient to express an excited electron (orbital) by an arrow such as $\rightarrow\!\!-^{*}$, at the same time indicating its symmetry type, i.e. the direction of the electron (charge) migration† (on one side of the nodal plane formed). Thus, the excited P^1 and P^3 states of the helium atom, in which the excited orbital has a nodal plane through the nucleus, may be expressed by III and IV respectively. Moreover, the representation of a normal excited state by a symbol, in which each unperturbed state is expressed by a separate formula, would, obviously, become much too involved in more complicated polyelectronic systems. It may, therefore, be suggested that they be replaced by one simplifying formula only, in which each unperturbed state is expressed by an arrow (indicating the excited electron involved). Thus, III and IV may be replaced by IIIa and IVa respectively. Such formulations have the additional advantage that they give a qualitative picture of the time-averaged electron migrations in the excited electronic system.

III $\overset{\rightarrow}{\underset{*}{\text{He}}} \leftrightarrow \overset{*}{\underset{\rightarrow}{\text{He}}}$ IIIa $\overset{\rightarrow}{\underset{\rightarrow}{\text{He}}}$ IV $\overset{\rightarrow}{\underset{*}{\text{He}}} \leftrightarrow \overset{*}{\underset{\rightarrow}{\text{He}}}$ IVa $\overset{\rightarrow}{\underset{\rightarrow}{\text{He}}}$

To be more precise, each unperturbed state will be assumed to include already the effect of perturbation arising from the different Coulomb repulsions of the electrons in the ground and excited state as distinct from the effect of that part of the perturbation attributed to "resonance" (for simple non-mathematical descriptive discussions of this matter, cf. also Heitler[14] and Pauling and Wilson[15]).

2. SINGLE BONDS (H_2) AND DOUBLE BONDS

The excited states of the hydrogen molecule are well understood.[16] Those of interest to the following discussion may be expressed in the terms of our qualitative analysis by V ($^1\Pi_u$), VI ($^1\Sigma_u$), VII ($^3\Pi_u$) and VIII ($^3\Sigma_u$) which, again, may be replaced by the simplifying symbols Va-VIIIa. Va and VIa appear in absorption (at approximately 1000 and 1100 Å respectively), whereas transitions from the ground state ($^1\Sigma_g$) to the more stable "triplet" states VIIa and VIIIa are forbidden by spin requirements as well as by the absence of a transition moment.



V Va VI VIa

VII VII a VIII VIII a

* This arrow has been chosen to distinguish it from the normal one widely used to indicate an inductive effect or spin. The direction of the arrow is not intended to indicate the change of the total charge distribution within an excited state, which would require also the consideration of the (out-of-phase) migration in the opposite direction, i.e. on the other side of the nodal plane (cf. also below).

† Spherically symmetrical excited orbitals, e.g. those corresponding to the S^1 and S^3 states of the helium atom, are forbidden in absorption and, being unimportant for the absorption spectra of organic molecules, may be ignored. The expression "migration" is used in place of "displacement," the latter being reserved for the movement of the maxima of absorption bands.

[14] W. Heitler *Elementary Wave Mechanics* Oxford University Press (1945).

[15] L. Pauling and E. B. Wilson *Introduction to Quantum Mechanics* p. 354. McGraw-Hill, New York (1935); R. S. Mulliken *J. Chem. Phys.* **7**, 20 (1939).

[16] G. H. Dieke and J. J. Hopfield *Phys. Rev.* **30**, 400 (1927); O. W. Richardson *Molecular Hydrogen and its Spectrum* University Press Yale (1934); G. Herzberg *Spectra of Diatomic Molecules* Van Nostrand, New York (1950); E. J. Bowen *Chemical Aspects of Light* pp. 89, 101. Clarendon Press, Oxford (1946); also *Ann. Rep. Chem. Soc. London* **40**, 16 (1943).

State V (Va) corresponds to the absorption system at shorter wavelengths and, since the bond axis lies in the nodal plane of the excited orbital, i.e. the charge migrates from both nuclei as in excited atoms, it is generally referred to as a Rydberg transition. We are, particularly, interested in state VI (VIa), which has a nodal plane perpendicular to the bond axis corresponding to an electron migration along this axis (*N–V* transition in Mulliken's terminology[17]), since this same type of transition is characteristic of the *R*-, *B*-, and *K*-bands of the more complicated organic molecules. Using valence bond terminology, this state has been qualitatively described as an ionic state $H^+H^- \leftrightarrow H^-H^+$.[15]

The spectra of ethylene and its homologues possess three band systems, at ~1650 Å (high intensity), at ~1750 Å (shoulder of moderate intensity) and above 2000 Å (observed in ethylene homologues and of very low intensity ($\varepsilon < 1$))[18, 19]. The two bands of higher intensity are generally recognised to be of the same type as the two band systems of the hydrogen molecule. Experimental evidence based on an analysis of the effect of substituents on these two bands supports the view that the band system at 1750 Å corresponds to a transition involving an electron migration along the bond-axis (*K*-band; *N–V* transition) and the superposed band system of higher intensity at 1650 Å to the Rydberg transition (perpendicular to the bond-axis).[20]

It is at this stage that our analysis, which (in agreement with views also expressed by Lewis and Calvin and by Lennard-Jones and Pople[12]) is based on the equivalency of the two electron pairs of a double bond, separates, in principle, from the widely held views which consider the interpretation of the spectrum only or mainly as a π electron problem. Whereas in the helium atom or the hydrogen molecule the two interacting electrons belong (in the ground state) to the same orbital, in ethylene the interaction now extends to the electrons of a second neighbouring orbital. Ignoring Rydberg transitions (perpendicular to the bond axis), this allows for four different normal excited states (IX–XII), each arising from resonance of the four unperturbed states of type XIII.

State IX corresponds to an allowed transition (of the *N–V* type) and, since it involves a migration of all electrons towards the same carbon nucleus, should be the least stable state (cf. below) responsible for the band system at 1750 Å (*K*-band). States X–XII will be more stable, but forbidden in absorption by change of spin (X, XI) and/or a negligible transition moment. One of these should be identified with the absorption band of very low intensity. The problem of ethylene reappears in all double bonds such as C:N, C:O, C:S, N:N, N:O, and NO:O which bonds, in addition

[17] R. S. Mulliken *J. Chem. Phys.* **3**, 375, 506, 514, 517, 564 (1935); **7**, 14, 20, 121, 339, 353, 356, 364 (1939).
[18] E. P. Carr, M. Walker and G. F. Walter *J. Chem. Phys.* **4**, 751, 756 (1936); E. P. Carr and H. Stücklen *J. Chem. Phys.* **4**, 760 (1936); **6**, 55 (1938); **7**, 631 (1939); *Z. phys. Chem.* B **25**, 57 (1934).
[19] W. Lüthy *Z. Phys. Chem.* A **107**, 285 (1923); C. P. Snow and C. B. Allsopp *Trans. Faraday Soc.* **30**, 93 (1934); G. Scheibe and H. Grieneisen *Z. Phys. Chem.* B **25**, 52 (1934). W. J. Potts, *J. Chem. Phys.* **23**, 65 (1955).
[20] A. Burawoy *Disc. Faraday Soc.* **9**, 78 (1950).

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to bands of higher intensity below approximately 2000 Å*, are again responsible for bands of very low intensity generally at considerably longer wavelengths ($\varepsilon < 20$ in simple derivatives).[1] In the absence of any evidence to the contrary, these *R*-bands may be considered to correspond to a transition of the same type since, as far as accessible to experimental test, they have been shown to obey the same very characteristic optical rules† (effect of substituents, of solvents and of proton addition).[1–3, also 21–24]

These bands have been assigned to transitions involving an excited triplet (radical) state,[1,3,4,25–27] i.e. originating in the bonding electrons, or to n–π transitions involving the non-bonding (unshared) electrons.[21,22,28] A critical analysis of the available experimental data (which has also taken into account numerous, as yet unpublished, observations) has already led to the conclusion that they all originate in the bonding electrons, which is certain for the *R*-bands of the ethylene derivatives.[3] On the other hand, the molecular extinction coefficients (ε) of these bands on suitable substitution of the double bonds reach values as high as 2000, which may make their interpretation as singlet-triplet transitions, forbidden both by spin requirements and by small transition moments, uncertain.

In contrast, state XII which symmetrically and probably energetically is similar to the (least probable) triplet state XI and which corresponds to an electron migration around a two-membered ring does not involve a change of spin and is "forbidden" only by the comparatively small transition moment. It is considered as an alternative and, indeed, the most likely interpretation for the low intensity *R*-bands (cf. below). It should be noted that the present analysis does not allow for a transition of the n–π type which matter will be more fully discussed elsewhere.

3. EFFECT OF TERMINAL GROUPS OF ABSORBING SYSTEMS ON *K*-BANDS

Empirical Conclusions

Recently,[5,6] experimental evidence has been given that the electron migration in one direction along an absorbing system such as XIV (the "effective" electron migration) determines the stability of the excited state corresponding to the *K*-band. It has also been shown[1,5,6] that the displacement of a *K*-band to longer wavelengths by structural modifications of the terminal groups (XIV, A—C or C—B) can be due to two factors:

(a) An electron-shift (in the ground state) of the substituted system which will increase its polarisability and facilitate the electron migration in this direction.

* This refers only to simple compounds such as formaldehyde, azomethane, nitrosobutane or nitromethane.

† Unfortunately, none of these tests can be applied to the ethylene *R*-bands.

[21] J. R. Platt *J. Chem. Phys.* **19,** 101 (1951); F. Halverson and R. C. Hirt *J. Chem. Phys.* **19,** 711 (1951).
[22] M. Kasha *Disc. Faraday Soc.* **9,** 14 (1950); G. J. Brealey and M. Kasha *J. Amer. Chem. Soc.* **77,** 4462 (1955).
[23] H. McConnell *J. Chem. Phys.* **20,** 700 (1952).
[24] A. Burawoy, M. Cais, J. T. Chamberlain, F. Liversedge and A. R. Thompson *J. Chem. Soc.* 3721 (1955).
[25] M. Kasha *Chem. Rev.* **41,** 401 (1947).
[26] E. P. Carr *Chem. Rev.* **41,** 293 (1947).
[27] G. N. Lewis and M. Kasha *J. Amer. Chem. Soc.* **67,** 934 (1945).
[28] R. S. Mulliken *J. Chem. Phys.* **3,** 564 (1935); H. L. McMurry and R. S. Mulliken *Proc. Nat. Acad. Sci.* **26,** 312 (1940); H. L. McMurry *J. Chem. Phys.* **9,** 231, 241 (1941).

(b) An increase of the polarisability of the terminal group itself.

XIV $\quad A—(CH=CH)_n—B \longrightarrow$

This is illustrated by a few simple examples in Tables 1 and 2. The *K*-bands of the *p*-nitrotoluene derivatives (XV), in which the effective electron migration of the transition is towards the nitro group, are displaced to shorter wavelengths, whereas those of the *p*-toluidine or 4-methoxy-4′-methyl diphenyl derivatives (XVI, XVII), in which the effective electron migration is towards the CH_2X group, are displaced to longer wavelengths as the electron attracting power (inductive effect) of the substituent X increases ($H < NH_2 < OH < Cl < CN < NH_3^+ < NO_2$). However, the electronic polarisability of the substituent CH_2X makes an additional contribution which, in the case of substituents of high polarisability, may become the dominating factor. Thus, in both the *p*-nitrotoluene and the 4-methoxy-4′-methyldiphenyl series, the *K*-bands are displaced to longer wavelengths in the order of substituents $CH_2Cl < CH_2Br < CH_2I$. It is noteworthy that in the latter series the red-shifts due to the CH_2Br and CH_2I groups (+172; +315 Å) are of the same order and greater respectively than that due to a $CH=CH_2$ group (+272 Å).

$O_2N—C_6H_4—CH_2X \longleftarrow$ XV $\qquad H_2N—C_6H_4—CH_2X \longrightarrow$ XVI $\qquad MeO—C_6H_4—C_6H_4—CH_2X \longrightarrow$ XVII

TABLE 1.—MAXIMA OF *K*-BANDS IN Å

A	*p*-$O_2N—C_6H_4—$A in hexane	*p*-$H_2N—C_6H_4—$A in ethanol	*p*-MeO—$C_6H_4—C_6H_4—$A in hexane
H	2513 (2595*)	2344	2595
CH_2NO_2	2513	—	—
CH_2NH_3	— (2620*)	2455	—
CH_2CN	2547	2424	2657
CH_2Cl	2581	—	2712
CH_2OH	2610	2410	2638
CH_2Br	2641	—	2767
CH_2NH_2	2651	2410	—
CH_3	2645	2355	2602
CH_2I	2649	—	2910
$CH=CH_2$	—	—	2867

* In ethanol.

Similarly, the *K*-bands are displaced to longer wavelengths in the order of substituents $F < Cl < Br < I$, not only in the case of the halogenobenzenes (XVIII) and *p*-nitrohalogenobenzenes (XIX), in which the halogens are at the "donating" end of the effective electron migration, but also in the case of the *p*-halogenoanilines (XX), in which they are at the "receiving" end. However, in the latter series the displacements are much smaller and the fluorine atom is responsible for a blue-shift. The polarisability of the C—Hal electrons is the dominating factor and is smaller towards the halogen atom than in the opposite direction.

Again, the contribution of the polarity factor is clearly shown (i) by the fact that the displacements of the *K*-bands on introduction of the halogen atoms are greater

in the *p*-nitrohalogenobenzenes (hexane: +56, 139, 184, 352 Å) than in the halogenobenzenes (+48, 132, 140, 280 Å), since the electron attracting nitro group is responsible in the ground state for electron shifts in the C-Hal systems towards the carbon atom, and (ii) by the fact that on replacing hexane by the more polar ethanol, the red-shifts due to the halogen atoms (cf. Table 2, D) are reduced in the two former and enhanced in the latter series.

$$\underset{\text{XVIII}}{\overset{\longleftarrow}{C_6H_5\text{—Hal}}} \qquad \underset{\text{XIX}}{\overset{\longleftarrow}{O_2N\text{—}C_6H_4\text{—Hal}}} \qquad \underset{\text{XX}}{\overset{\longrightarrow}{H_2N\text{—}C_6H_4\text{—Hal}}}$$

TABLE 2.—MAXIMA OF *K*-BANDS IN Å

X	C_6H_5—X			*p*-O_2N—C_6H_4—X			*p*-H_2N—C_6H_4—X		
	hexane	ethanol	D	hexane	ethanol	D	hexane	ethanol	D
H	~2020	~2030	—	2513	2595	—	2340	2344	—
F	2068	2068	−10	2569	2622	−29	2305	2334	+25
Cl	2152	2130	−32	2652	2699	−35	2414	2445	+27
Br	2160	2135	−35	2697	2755	−24	2418	2452	+30
I	2300	2275	−35	2865	2940	−7	2463	2502	+35

It may be noted that the electrons of the halogen atoms in the CH_2X groups of the systems XVI and XVII and in the *p*-halogenoanilines (XX) (and related series), in which the halogen atoms are at the "receiving" end of the effective electron migration, participate in the transition. This cannot be accounted for by a consideration of π electrons only and of mesomeric (electromeric) electron displacements. The hypsochromic effect of the fluorine atom in *p*-fluoroaniline (and related series) can only be explained by a smaller polarisability of the C—F electrons towards the fluorine atom as compared with that of the C—H electrons. This clearly demonstrates that even the latter participate in the electron migration of the *K*-band transition.

Theoretical analysis

The theoretical analysis may now be extended to the effect of the electrons of the terminal groups (A—C or C—B) of ethylene or, indeed, of any other absorbing (conjugated) system (XIV) on the corresponding *K*-bands. The qualitative consideration of the mathematically well-established effects resulting from perturbations attributable to Heisenberg resonance affords a consistent theoretical interpretation of the empirical conclusions summarised above.

Most organic molecules (even conjugated hydrocarbons) contain covalent linkages of a varying degree of polarity, which fact is known to offer considerable difficulties to the mathematical treatment of molecular states and limits its scope. In contrast, the present qualitative analysis is able to take full account of this important property of covalent linkages.

XXI

The normal excited state corresponding to a *K*-band can be represented as a "hybrid" *of unperturbed states each involving one excited electron.* The contribution of each of the $(2 + 6n)$ unperturbed states (again, indicated for convenience by one formula XXI) to the "hybrid" will be proportional to their stability. States involving neighbouring excited electrons will interact.

The excited orbital of each unperturbed state is divided by an (additional) nodal plane into two parts corresponding to wave-functions of opposite sign. In an unsymmetrical bond, it will extend more to one side of the nodal plane, i.e. the probability of finding the electron in this more stable part-orbital will be greater. In valence bond terminology, this would be equivalent to the statement that in the excited state of a molecule AB described as a hybrid $A^+B^- \leftrightarrow A^-B^+$ the stability and contribution to the hybrid of A^+B^- is different from that of A^-B^+. The present qualitative analysis is independent of the valence bond or molecular orbital description of localised bonds and of unperturbed excited states. These descriptions are known to represent only different mathematical methods of approximation (in terms of atomic orbitals), i.e. their distinction has only a mathematical and no real physical significance.

The *degree of interaction* will increase, the lower and the energetically nearer each pair of interacting (unperturbed) energy levels are, but, in the first instance, only their part-orbitals in phase with the effective electron migration of the transition, the direction of which is indicated by the arrows, will be important. Thus, if A and B in XXI are identical, e.g. halogen or hydrogen atoms, the unperturbed energy levels involving the excited electrons of the unsymmetrical bonds A—C and C—B will be equal. However, the degree of interaction (determining the degree of stabilisation of the normal excited state), will be different since it depends on the different extension (stability) of the excited orbital in the two directions of these bonds, i.e. on both sides of the dividing nodal plane.

It is realised that the degree of interaction (in the excited state) will also depend on the distance (degree of repulsion) between the interacting electrons, e.g. on the size of the common atom or on the angle formed by the orbitals, but in the qualitative comparison of the varying effects of terminal atoms or groups within the same series (XXI, A or B), this effect may be neglected.

The factors determining the *stability* of the normal excited state are (i) the most stable (the "basic") unperturbed excited state and (ii) the degree of its interaction with the unperturbed states involving excited neighbouring electrons. Again, the stability of the latter will be modified by interaction with other neighbouring states, the effect of which is transmitted (in a diminishing degree) along the whole absorbing system. (In this connection, cf. the interesting mathematical treatment of the excited states (corresponding to the *K*-bands) of *p*-polyphenyls by Murrell and Longuet-Higgins,[29] who have shown that even in absence of delocalisation between the electron systems of the phenyl groups, their interactions would account semiquantitatively for the observed band displacements.)

According to this view, in a system such as C=C—C=C, the *direct* interaction of the unperturbed energy levels involving the excited electrons of one double bond with those involving the excited electrons of the other is considered to be of secondary importance. Moreover, the transmitted effect in a system such as C=C—C—C=C,

[29] J. N. Murrell and H. C. Longuet-Higgins *J. Chem. Soc.* 2552 (1955).

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in agreement with experience, is much smaller because the interaction of the transmitting states, which involve excited electrons of the single C—C bonds, and which are of low stability compared with the basic unperturbed state, is only small.[5] It should be noted, however, that the *contribution* to the hybrid of the unperturbed states involving the excited electrons of each double bond will be of the same magnitude.

A more precise definition of the conclusion arrived at empirically that the electron migration in one direction of the absorbing system determines the stability of the normal excited state can now be given. It indicates that the additional stabilisation arising from the interactions of the part-orbitals corresponding to the complementary electron migration of the system is only negligible, although it has to be taken into account even in qualitative comparative discussions, if only very small differences are involved.[6] A fuller experimentally supported discussion of this matter will be given elsewhere.

Our investigations have also shown that any electron shift in the ground state of an absorbing system or individual bond (as, for example, caused by a change of the terminal group or by a solvent) increases the electron polarisability in this direction (and reduces it in the opposite direction) and, thus, dependent on the direction of the effective electron migration of the transition, stabilises or otherwise the normal excited state. This indicates that in each bond the increased stability of the (unperturbed) part orbital in phase with the effective electron migration (which results from both the reduction of the ionisation potential of the "donating" atom and/or the increase of the electron affinity of the "receiving" atom*) is the determining factor. It is also more important than the increased destabilisation to be expected from the accompanying increased interaction of the two part orbitals corresponding to the electron pair forming the bond.

4. EFFECT OF SIDE-CHAIN SUBSTITUENTS ON *K*-BANDS

An analysis of the electronic transitions corresponding to *K*-bands is not complete without consideration of the most characteristic and very different effects of substituents in a branch (side-chain) of the main absorbing system. These effects represented an important part of the evidence advanced by the author for his original classification of electronic spectra, but, in more recent years, they have been almost completely neglected and their significance generally not realised.

As illustrated by the examples of a few carbonyl and thiocarbonyl derivatives in Table 3, replacement of a branching hydrogen atom by a methyl group may now cause a blue-shift (acetophenone, −40 Å; diphenylyl methyl ketone, −70 Å), by a phenyl group only a small red-shift (benzophenone, +72 Å; diphenylylphenyl ketone, +32 Å) which is only very slightly enhanced by a diphenylyl group (bisdiphenylyl ketone, +65 Å). Replacement by an amino or hydroxyl group or a charged oxygen atom (in anions) may cause appreciable blue-shifts on direct substitution (benzamide, −200 Å; benzoic acid, −159 Å; benzoate anion, −213 Å) and smaller displacements in aromatic (side-chain) substituents. This is in contrast to the always bathochromic and generally much greater effects of these atoms or groups in

* In the case of unshared (non-bonding) electrons, only one of these factors is relevant.

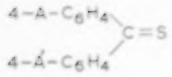
terminal positions of an absorbing (conjugated) system.[1,2,5,6,30–32] Thus, the *K*-band of thiobenzophenone (XXII, A = A′ = H) is displaced very strongly to longer wavelengths (375, 395 and 1205 Å respectively) on introduction of one phenyl, hydroxyl or dimethylamino group into the first and terminal para position (XXII, A = Ph, OH, NMe_2; A′ = H), whereas the effect of these groups on introduction into the para position of the second (branching) phenyl group (XXII, A′ = A) is very small and often in the opposite direction (+10, −85, −70 Å respectively).

TABLE 3.—COMPARISON OF THE EFFECT OF SUBSTITUENTS ON *K*- AND *R*-BANDS

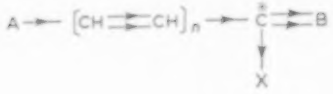
Substance	Solvent	X	*K*-band		*R*-band	
			λ_{max}, Å	ε	λ_{max}, Å	ε
$C_6H_5.C(X):O$	hexane	H	2408	14,000	3280	28†
	hexane	Me	2368	14,000	3210	44
	hexane	Ph	2480	20,000	3440	100
	ethanol	H	2445	13,000	—	—
	ethanol	OH	2286	14,500	—	—
	ethanol	NH_2	2245	13,500	—	—
	+0·1% NaOEt	O^-	2232	11,000	—	—
$Me.C(X):O$[33]	water	Me	—	—	2645	17
	water	OH	—	—	2035	40
	water	NH_2	—	—	2040*	200
	water	O^-	—	—	2000*	—
$C_6H_5.C_6H_4.C(X):O$	ethanol	H	2895	23,000	—	—
	ethanol	Me	2820	28,000	—	—
	ethanol	Ph	2912	26,000	—	—
	ethanol	$C_6H_4.Ph$	2977	42,000	—	—
$C_6H_5.C(X):S$	benzene	Ph	3195	17,000	6065	210
$(4\text{-})Ph.C_6H_4.C(X):S$	benzene	Ph	3570	18,100	6087	260
			3365	16,000		
	benzene	$C_6H_4.Ph$	3580	28,000	6110	300
$(4\text{-})HO.C_6H_4.C(X):S$	benzene	Ph	3590	13,800	5930	240
	benzene		3270	11,400		
	benzene	$C_6H_4.OH$	3505	23,000	5885	340
$(4\text{-})Me_2N.C_6H_4.C(X):S$	benzene	Ph	4400	23,400	5837	380
			3350	11,000		
	benzene	$C_6H_4.NMe_2$	4330	40,000	5750	900

* Inflexion.
† Fine structure.

[30] K. Bowden, E. A. Braude and E. R. H. Jones *J. Chem. Soc.* 948 (1946).
[31] E. A. Braude *Ann. Rep. Chem. Soc. London* **42**, 105 (1945).
[32] L. Doub and J. M. Vandenbelt *J. Amer. Chem. Soc.* **69**, 2714 (1947).
[33] H. Ley and B. Arends *Z. Phys. Chem.* **B 17**, 177 (1932); G. Scheibe *Ber. Dtsch. Chem. Ges.* **58**, 586 (1925).



XXII



XXIII †

The effect of these substituents is due to the same two factors shown to be responsible for the effect of terminal groups, i.e. (i) a change of polarisability (stability of the unperturbed excited states) of the substituted system due to electron shifts in the ground state, and (ii) the degree of the electronic polarisability of the substituent, but both factors are now of much greater complexity.

Thus, in the most common system of the general type XXIII, an electron repelling group such as methyl (X = Me) will cause electron shifts in the ground state towards both A and B. This will inhibit the effective electron migration (from A to B) in the former and facilitate it in the latter branch of the (main) absorbing system. The separation of the electrons at the substituted (starred) carbon atom in the ground state will also reduce the degree of their interaction in the excited state, which effect will be similar to that which might result from any inhibition of "conjugation" by intramolecular steric hindrance (for a tentative interpretation of the latter effect based on molecular structures containing localised bonds only, see Burawoy and Chamberlain[10]).

The blue-shifts observed on introduction of the branching electron repelling methyl, hydroxyl, and amino groups and charged oxygen atom in anions (XXIII, X = Me, HO, NH_2, O^-) should be accounted for by these factors.

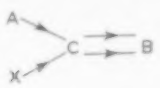
The participation of the electrons of the side-chain substituent (see XXIII, X) in the electron migration of the transition will have an additional, again rather complex effect (consisting of the stabilisation of one branch and destabilisation of the other) on the stability of the excited state. Detailed systematic investigations aiming at the difficult separation of the various effects, which depend to a high degree upon the individual substituted systems, will be reported elsewhere.

However, an unambiguous experimental solution of the more fundamental problem of the direction of the effective electron migration within the side-chain is possible. This direction is governed by the principle that by far the most stable excited state is obtained, if the effective electron migration towards a nucleus is accompanied by a recession of all the other electrons away from it (as shown in XXIII). Elsewhere, this conclusion will be confirmed by an analysis of the effect of such substituents, but it is already strongly supported by the following absolute observations.

In a system such as A—CX=B, in which the main effective charge migration (towards B) is certain, a charge migration in the branch C—X towards the carbon atom would allow for only one electronic transition (XXIV), whereas in the alternative case two similar electronic transitions could be expected (XXV and XXVI). They would be responsible for two *K*-bands which, in favourable conditions, i.e. if sufficiently separated, would be capable of observation. The latter is in agreement with

† Subsequently, for convenience, the symbols will be further simplified. The arrow —→ will be used to indicate the combined "unperturbed" state involving the electron pair of each single bond.

experience. (This does not exclude a possible existence of *K*-bands corresponding to an excited state XXIV, to be expected at considerably shorter wavelengths.)

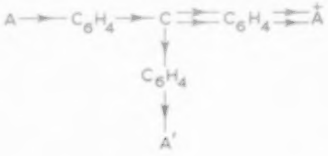


XXIV

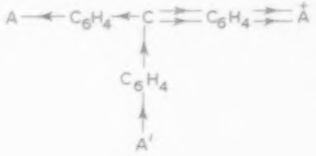
XXV

XXVI

The author,[34] in discussing the competition between the various absorbing systems of an organic molecule, has shown that the spectra of di-substituted *pp'*-triphenylmethyl ions possess two *K*-bands. They could be assigned to the two absorbing conjugated systems present and, in the light of the present discussion, correspond to the excited states XXVII and XXVIII (A = NMe_2, OMe, SMe, Ph; A′ = H). In contrast, all *pp'p"*-trisubstituted derivatives (A′ = A), in which both excited states become equivalent, are responsible for the appearance of only one band of increased intensity. The different direction of the electronic vectors of the transitions corresponding to the two *K*-bands of Malachite Green (XXVII and XXVIII, A=NMe_2; A′=H) observed by Lewis and Biegeleisen[35] is in agreement with our interpretation.

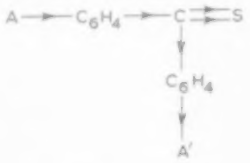


XXVII

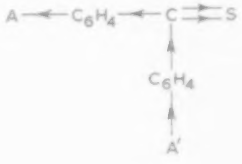


XXVIII

The examples of the thiobenzophenone derivatives (cf. Table 3) were chosen to illustrate the same point. Again, the spectra of mono-*p*-substituted derivatives show two *K*-bands corresponding to the two excited states XXIX and XXX (A = Ph, OH, NMe_2; A′=H), whereas *pp'*-disubstituted derivatives (A′ = A) are responsible for only one band of higher intensity, both excited states now being equivalent.



XXIX



XXX

5. *K*-BANDS OF ETHYLENE AND BENZENE

The preceding analysis shows that the excited state responsible for the *K*-band of ethylene or any other absorbing system can be represented by XXXI (*e*, "effective" and *c*, "complementary"). It is noteworthy that although ethylene (A = B = H; *n* = 1) is symmetrical in the ground state, according to this view this is no longer true for the (four possible equivalent) excited states. Similarly, the (six possible equivalent) excited states responsible for the *K*-band of benzene (A = B = H) at approximately 2030 Å are represented by XXXII (*e* and *c*), again indicating some

[34] A. Burawoy *Ber. Dtsch. Chem. Ges.* **64**, 473, 1635 (1931).
[35] G. N. Lewis and J. Biegeleisen *J. Amer. Chem. Soc.* **65**, 2102 (1943).

distortion of the electronic system. The effective electron migration in the two branches of the benzene system towards the same (starred) carbon atom is unavoidable. This results in an appreciable destabilisation which should account for the as yet unexplained, most characteristic fact that the *K*-band appears at appreciably shorter wavelengths than that of 1:4-dimethylbutadiene (2270 Å), *cyclo*hexa-1:3-diene (2560 Å) and similar compounds.

XXXI

XXXII

As recently shown,[10,24,36] in agreement with this interpretation, the *K*-bands of mono-substituted benzene derivatives such as diphenyl, azobenzene, benzaldehyde, nitrosobenzene, and nitrobenzene (XXXII, A = Ph, N:N.Ph, CH:O, N:O, NO_2, B = H) are only slightly displaced to longer wavelengths on introduction into the branching *ortho* and *meta* positions of substituents such as the amino, hydroxyl, and thiol groups which have very appreciable effects in the terminal para position (B = NH_2, OH, SH). This is also illustrated in Table 4 for the effect of methyl, chlorine, methoxyl and charged oxygen substituents on the *K*-band of benzaldehyde.

XXXIII XXXIV

The spectra of the *m*- and *o*-formylphenoxide ions show two *K*-bands at approximately 2600 Å and 2400 (2300) Å respectively, which correspond to the *K*-bands of benzaldehyde (2445 Å) and of the phenoxide ion (2374) Å, i.e. to the excited states indicated by XXXIII and XXXIV. This is characteristic of numerous *m*- and *o*-disubstituted benzene derivatives. A detailed discussion of this matter and of the problem of the theoretically possible normal excited states of a molecule rather than those detectable by the favourable positions and intensities of the corresponding absorption bands is outside the scope of this paper.

Theoretical (mathematical) treatments and discussions of the spectrum of benzene, based on its regular hexagon structure and the simplifying consideration of the π electrons only, have led to the assignment of the 2000 Å band to a forbidden

[36] A. Burawoy and J. T. Chamberlain *J. Chem. Soc.* 3734 (1952).

TABLE 4.—MAXIMA OF *K*- AND *B*-BANDS OF SUBSTANCES; $X.C_6H_4.CH{:}O$ IN ETHANOL

X		*K*-band			*B*-band		
H	λ_{max}Å		2,445			2,805	
	ε		13,000			1,250	
		p-	*m*-	*o*-	*p*-	*m*-	*o*-
Me[37]	λ_{max}	2,550	2,482	2,495	2,800†	2,894	2,925
	ε	12,500	11,000	12,500	—	1,350	1,700
Cl	λ_{max}	2,544	2,442	2,489	2,800†	2,920	2,980
	ε	16,000	12,500	10,000	—	1,300	1,600
OMe[19]	λ_{max}	2,765	2,525	2,528	—*	3,087	3,210
	ε	15,500	9,500	10,500	—	3,000	4,550
O^-	λ_{max}	3,323	(i) 2,610†	2,613	—*	3,598	3,790
	ε	28,000	6,000	6,300	—	2,400	6,400
			(ii) 2,404	2,310			
			19,000	16,000			

* *B*-band not observed being masked by *K*-band.
† Inflexion.

transition or to a Rydberg transition.[18,26,38,39] However, its identification as a *K*-band (involving an allowed transition of the *N*–*V* type) is unambiguously established by the very considerable experimental evidence based on the study of the effect of substituents and is already widely accepted by experimentalists.[10,32,40] (For the assignment of the 1800 Å band of benzene to a Rydberg transition, compare references 20, 39, 41).

6. QUALITATIVE EFFECT OF PERTURBATION DUE TO RESONANCE

In view of the difficulty, if not impossibility of a quantitative mathematical treatment of the complex excited states under discussion, it is fortunate that the effect of the perturbation resulting from resonance is qualitatively clear. It corresponds to a change of the effective nuclear charges (the ionisation potentials and electron affinities respectively) in the observed excited states. Thus, the arrows suggested to indicate the individual unperturbed excited states of an absorbing system and the direction of the effective charge migration obtain an additional qualitative, but significant meaning. They can be taken to indicate the ("time-averaged") change of the effective nuclear charges due to the resonance and the resulting stabilisations or destabilisations respectively of the normal excited state.

[37] E. A. Braude and F. Sondheimer *J. Chem. Soc.* 3754 (1955). For data in hexane solution.
[38] H. Sponer, G. P. Nordheim and E. Teller *J. Chem. Phys.* **8**, 455 (1940); A. L. Sklar and M. Goeppert-Mayer *J. Chem. Phys.* **6**, 645 (1938).
[39] V. J. Hammond, W. C. Price, J. P. Teegan and A. D. Walsh *Disc. Faraday Soc.* **9**, 53 (1950).
[40] G. N. Lewis and M. Calvin *Chem. Rev.* **25**, 303 (1939); A. D. Walsh *Ann. Rep. Chem. Soc., London* **44**, 39 (1947).
[41] W. C. Price and A. D. Walsh *Proc. Roy. Soc.* A **191**, 22 (1947).

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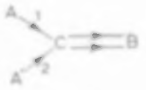
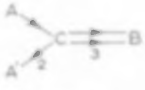
In the excited state of the hydrogen molecule VI, the arrows indicate an increase of the effective nuclear charge (and ionisation potential) at one hydrogen atom and decrease of the effective nuclear charge (and its electron affinity) at the other as compared with those in the unperturbed states, both factors destabilising the normal excited state, whereas in the triplet state VIII the opposite effects occur, corresponding to stabilisation. Similarly, in ethylene, combining for convenience each electron pair as a unit, the state IX, corresponding to the *K*-band, is less stable and state XII, corresponding to the *R*-band, is more stable than the (combined) "unperturbed" state involving one excited electron pair only, which is in agreement with the appearance of *R*-bands at longer wavelengths. (This is only valid for simple compounds, since substituents, very considerably and to a different degree, modify the energy levels corresponding to *R*- and *K*-bands.)

Again, the arrows representing the unperturbed excited states of the electrons of the terminal groups A—C and C—B of ethylene or any other more complicated absorbing system (XXI) indicate an increase of the electron density at C_{-A} and a decrease at C_{-B}, i.e. a reduction of the ionisation potential at the former and increase of the electron affinity at the latter, both resulting in stabilisation.

Finally, the principle that the observed excited state is more stable if an electron migration towards a nucleus is accompanied by recession of the other electrons (including those in a side-chain), indicates that the destabilisation resulting from a reduced electron affinity as in XXXV (migration of 1 and 2 towards C) is considerably greater than any resulting from an increased ionisation potential as in XXXVI (migration of 2 and 3 from C). Qualitatively, this is just what could be expected, since the interacting part orbitals in the former case are much closer (in space) than in the latter.



XXXV



XXXVI

7. *R*-BANDS

Earlier investigations[1,3] have already shown that the apparently complex observations related to *R*-bands can be reduced to two simple generalisations:

(a) Substituents of the chromophoric double bonds have most characteristic effects on *R*-bands which are qualitatively similar to those of substituents (in a side-chain) of an absorbing conjugated system on *K*-bands. The examples shown in Table 3 have been chosen to illustrate this analogy. Again, a methyl group causes a blue-shift, a phenyl group only a moderate red-shift which is only insignificantly enhanced by a diphenylyl group, an amino or hydroxyl group or the charged oxygen atom blue-shifts which are particularly strong on direct substitution.

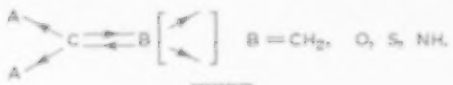
(b) *R*-bands are displaced to shorter wavelengths by influences (solvent effect, proton addition) which increase the polarity of the absorbing system.

The interpretation of the electron transition responsible for *R*-bands (see XII) advanced in this paper accounts for these observations*:

(a) The two electron pairs of a double bond can be compared with the two

* In principle, this does not exclude the triplet state X which would allow for a slightly modified analysis.

branches of a substituted absorbing conjugated system responsible for *K*-bands. The substituents will not only modify the polarity of the double bond in the ground state, but (like side-chain substituents of systems reponsible for *K*-bands) also participate in the transition. The direction of the effective electron migration is, again, towards the substituents (A), in agreement with the principle that by far the most stable excited state is obtained if a charge migration towards a nucleus is accompanied by a recession of all other participating electrons (cf. e.g. XXXVII).



XXXVII

(b) An increase of the polarity of the double bond will correspond to an electron shift in both bonds. This will stabilise the "effective" part orbitals of the unperturbed states involving the excited electrons of one bond, but destabilise those of the other bond and, thus, reduce their degree of interaction. In the absence of any quantitative analysis, no prediction of the resultant effect is possible. However, what should be more important, the stabilisation arising from the interaction of the electron pair of the double bond migrating towards C with that of a C—A bond, both being shifted (as the polarity of the system increases) against the direction of the effective electron migration, will certainly be reduced. This will enhance (or, if opposing, mask) the former effect and, thus, be mainly responsible for the blue-shift of the *R*-band. A more detailed discussion of the (physically) rather complex effect of substituents on the position of *R*-bands will require systematic investigations not yet available or, if possible, a semi-quantitative mathematical analysis of the matter.

8. BENZENOID-(B^{21}-) BANDS

As recently pointed out, the *B*-bands originate in the same type of electronic transition as the *K*-bands, but correspond to electronic migrations around the conjugated system formed by all three benzene double bonds.[24] This is supported by an analysis of the spectra of disubstituted benzene derivatives which shows that substituents in *ortho* position to each other are now terminal groups of the absorbing system. Thus, in contrast to the *K*-bands, the (in many cases masked) *B*-bands of diphenyl, azobenzene, benzaldehyde, nitrosobenzene, and nitrobenzene are strongly displaced to longer wavelengths on introduction of an amino, hydroxyl or thiol group into the *ortho* position, whereas in the branching *meta* and, in particular, in the *para* position these substituents have much smaller effects.

This is also shown by the spectra of the substituted benzaldehydes reported in Table 4, again chosen to illustrate simultaneously the different behaviour of the *K*-bands, in which case the *para* position is terminal and the *meta* and *ortho* positions are branching. The *B*-bands of the *para* substituted benzaldehydes are partly or completely masked by the *K*-bands of higher intensity, but a comparison of the spectra of benzaldehyde and of *p*-methyl-, *p*-chloro-, and *p*-methoxy-benzaldehyde respectively indicates that these substituents are responsible for slight hypsochromic shifts (for the similar effect of the *p*-methoxy group in 2:4-dimethoxy-1-nitroso-benzene, cf. reference 24, Fig. 1).

The excited state of disubstituted benzene derivatives corresponding to a *B*-band

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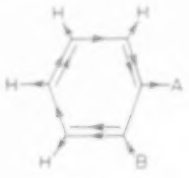
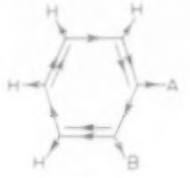
can, thus, be described by XXXVIII. That of mono-substituted benzene derivatives such as phenol or aniline (B = OH, NH_2; A = H) should be similar, but the possibility of a slightly modified excited state XXXIX for benzene itself and derivatives such as nitrobenzene or benzaldehyde (A = H, NO_2, CH:O; B = H) cannot be experimentally excluded and, indeed, may be more likely. The generally lower intensity of the *B*-bands (ε, ~ 100–7000) as compared with that of the *K*-bands (ε, ~ 5000–200000) is accounted for by the smaller transition moments due to the charge migration around the benzene ring.



XXXVIII



XXXIX

Although this interpretation of the *B*-band transition is well supported by experimental evidence, a more detailed analysis of the complex effect of substituents cannot be given briefly.

9. CONCLUSION

The wave-mechanical resonance characteristic for the excited states of all poly-electronic systems involves a complicated fluctuation ("time-averaged" distribution) of the transition energy. In this sense, it represents a definite physical phenomenon which is absent in ground states. Although the mathematical method of approach is similar, this has, as a phenomenon, nothing in common with the well-known applications of the valence-bond method to the interpretation of the stability of ground states. Thus, the latter may be accounted for without reference to "resonance", whereas excited states cannot.

Already, for this reason, the stability of an excited state cannot and does not show a simple relationship to that of the corresponding ground state.[6*] This also represents the justification for the present interpretation which considers the energy difference between the ground and normal excited states only, the energy of the former always being taken as zero (for a related discussion of this matter, cf. Simpson[42]).†

In the well-known simplifying, but in the author's view unjustified, application of the conception of resonance among several valence-bond structures to the (non-mathematical) interpretation of the constitutive changes in molecular structures, the contribution to the resonance hybrid of the various, often arbitrarily chosen, idealised ("unperturbed") states has been assumed to be a function of their relative stability and taken as a measure of the ensuing resonance (stabilisation) energy, the unknown magnitude of the resonance integrals not being considered. It should, therefore, be emphasised that in the present interpretation of *excited states*, the

* This follows already from the fact that the positions of the individual absorption bands of any particular substance are affected differently on introduction of a substituent or by a change of solvent.

† A classical analogue would be a system of coupled harmonic oscillators at rest (ground state) and in their normal modes of vibration (excited states).

[42] W. T. Simpson *J. Amer. Chem. Soc.* 77, 6164 (1955).

degree of interaction generally does not coincide with the contribution of the unperturbed excited states to the hybrid; that it may cause destabilisation as well as stabilisation, and that there is no freedom of choice once the electron migration of the transition is experimentally established.

The theoretical analysis outlined in this paper shows that the empirical conclusions derived from systematic experimental investigations of electronic spectra, when based on molecular structures built up of localised bonds only, can be consistently accounted for with the help of well-established wave-mechanical principles. It offers a qualitative, but very detailed understanding of electronic spectra of complicated polyatomic organic molecules[5,6] not attainable by mathematical treatments aiming at quantitative evaluations of spectroscopic data.‡

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The interpretation of electronic perturbations in an *excited state* as a wave-mechanical resonance phenomenon owed its success and justification to the ability to account qualitatively for the previously unexplained experimental fact that the He atom forms two systems of energy levels and for perturbations observed in atomic spectra in general, rather than to its quantitative aspect. This is also true for Mulliken's fundamental analyses of the structures and electronic spectra of simple molecules.

Similarly, an analytical approach to the complicated problems related to the electronic spectra of more complex polyatomic molecular structures, e.g. more detailed wave-mechanical formulations or mathematical analyses of principles possibly based on simple models, should make a greater contribution to the understanding of these problems than attempts at speculative mathematical evaluations of spectral data. The present qualitative analysis, which has taken into account all known relevant data, is accessible to experimental test and may serve as a guide for further systematic investigations, should offer a useful basis.

If not otherwise stated, the spectra of the carbonyl compounds are new determinations obtained with a Hilger E3 quartz spectrograph fitted with a Spekker photometer, those of the thiobenzophenone derivatives with a Hilger Uvispek Photoelectric Spectrophotometer. The latter have been selected from an unpublished extensive investigation carried out by Dr. P. Brocklehurst. This and the help given by Dr. A. R. Thompson in the preparation of this paper are gratefully acknowledged.

‡ In this connection, reference should be made to the very detailed, critical and significant, analysis of the mathematical approach and its limitations to the problems of molecular structures and, in particular, of excited states by Kauzmann.[43]

[43] W. Kauzmann, Quantum Chemistry, pp. 375–478. Academic Press, New York (1957).

Tetrahedron, 1958, Vol. 2, pp. 140–150. Pergamon Press Ltd., London

UNTERSUCHUNGEN ÜBER FURAN-VERBINDUNGEN—V

ÜBER DIE HERSTELLUNG UND KONFIGURATION VON EINIGEN FURYL-KETOXIMEN*

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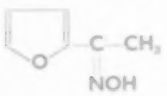
(*Received* 2 *July* 1957)

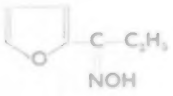
Zusammenfassung—Es wurden einige *syn*, *anti*-Furyl-ketoximpaare hergestellt, welche auch durch ihre Acetate, Benzoate und *p*-Toluolsulfonate charackterisiert wurden. Die Konfiguration der Ketoxime konnte auf chemischem Wege und auf Grund ihrer UV-Spektren bestimmt werden.

Abstract—Several pairs of *syn* and *anti*-furyl-ketoximes have been prepared, which have been characterised by their acetates, benzoates and *p*-toluenesulphonates. The configurations of the ketoximes were successfully established by chemical means and by their u.v. spectra.

ZUR Fortsetzung unserer Studien über die Umwandlungen von Furyl-ketoximen[1,2,3,4], war die Herstellung und Konfigurationsbestimmung der folgenden *syn*, anti-Furyl-ketoxim-Paare notwendig: Furyl-2-methyl-(I), Furyl-2-äthyl-(II), 5-Methylfuryl-2-methyl-(III), Furyl-2-phenyl-(IV), Benzofuryl-2-methyl-(V), Benzofuryl-2-phenyl-ketoxim (VI),



I



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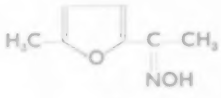

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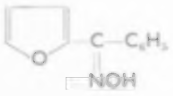
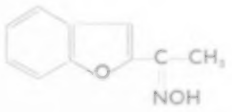
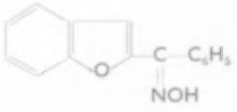


IV



V



VI

Von den beiden möglichen Stereoisomeren dieser Oxime ist in der Literatur nur die eine Modifikation erwähnt, von denen sich jedoch einige (III, IV, V) im Laufe unserer Versuche als Gemische erwiesen. Es lässt sich übrigens beim Durchsehen der Literatur feststellen, dass Ketoxim-Isomerenpaare verhältnismässig in kleiner Zahl beschrieben sind und selbst das Acetophenonoxim nur in einer Modifikation bekannt ist. Tabelle 1 zeigt die in der Literatur angegebene Schmelzpunkte der aufgezählten

* Im Auszug vorgetragen auf der Tagung der Chemischen Gesellschaft in der DDR am 22, Oktober 1955, zu Leipzig.

[1] L. Vargha, J. Ramonczai und P. Bite *J. Amer. Chem. Soc.* **70**, 371 (1948).
[2] L. Vargha, J. Ramonczai und J. Bäthory *J. Amer. Chem. Soc.* **71**, 2652 (1949).
[3] J. Ramonczai und L. Vargha *J. Amer. Chem. Soc.* **72**, 2737 (1950).
[4] L. Vargha und F. Gönczy *J. Amer. Chem. Soc.* **72**, 2738 (1950).

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TABELLE I

Ketoxim	Schmp.	Acetat Schmp.	Benzoat Schmp.	*P*-Toluol-sulfonat Schmp.	Literatur
Furyl-2-methyl-ketoxim(I)	104°	96°	97–98°	80°	1, 5, 6
Furyl-2-äthyl-ketoxim(II)	77°	—	—	68°	4, 7
5-Methyl-furyl-2-methyl-ketoxim(III)	78–79°	—	—	112°	4
Furyl-2-phenyl-ketoxim(IV)	132–133°	68°	—	118°	4, 8, 9
Benzofuryl-2-methyl-ketoxim(V)	154–155°	—	—	100–102°	2, 10
Benzofuryl-2-phenyl-ketoxim(VI)	132°	—	—	118°	4, 11, 12

Ketoxime, bzw. die Schmelzpunkte ihrer Acetate, Benzoate und *p*-Toluolsulfonate (Tosylate), soweit sie bekannt waren.

Über die Konfiguration der erwähnten Oxime-mit Ausnahme von (IV) und (VI)-liegen keine Anhaltspunkte vor. Die Oxime (IV) und (VI) dürfen auf Grund ihrer Beckmann'schen Umlagerung nach Untersuchungen von Vargha und Gönczy[4] (Bildung von Aniliden der Furan-, bzw. Benzofuran-carbonsäure) als *syn*-Furyl-ketoxime angesehen werden.

Zur Herstellung von einheitlichen Oximen gibt es kein allgemein anwendbares Verfahren. Im Laufe unserer Versuche konnten die aufgezählten Oximpaare durch Anwendung der folgenden 4 Methoden in einheitlichem Zustand erhalten werden.

(1) Unter gewissen Versuchsbedingungen bildeten sich manche Ketoxime in einheitlicher Form.

(2) Aus einigen in Form von Gemischen entstandenen Oximen liess sich das eine Isomere durch fraktionierte Krystallisation abtrennen.

(3) Nach Acetylierung des Oximgemisches trennte man die isomeren Acetate durch fraktionierte Krystallisation und erhielt das einheitliche Oxim mit vorsichtiger Hydrolyse seines Acetates.

(4) Manche reine Ketoxime liessen sich durch Behandeln mit Salzsäure in Äther quantitativ ins andere Isomere überführen, *syn*, *anti*-Isomerengemische konnten auf diese Weise stets in einheitliche Form gebracht werden.

Die Darstellungsweise der einzelnen Furylketoxime, welche auch durch ihre Acetate, Benzoate und Tosylate charakterisiert wurden, ist im Versuchsteil ausführlich beschrieben.

Die zur Bereitung der Oxime gebrauchten Ketone wurden in allgemeinem nach Literaturangaben hergestellt, nur die Herstellung des Furyl-2-äthyl-ketons und des 5-Methyl-furyl-2-methyl-ketons geschah abweichend, und zwar in Analogie zum

[5] S. S. Sandelin *Ber. Dtsch. Chem. Ges.* **33**, 492, 1176 (1900).
[6] H. A. Torrey und J. E. Zanetti *J. Amer. Chem. Soc.* **44**, 391 (1910).
[7] B. L. Emling, J. E. Beatty und J. R. Stevens *J. Amer. Chem. Soc.* **71**, 704 (1949).
[8] R. Marquis *Bull. Soc. Chim., Fr.* **3**, 23, 32 (1900).
[9] J. Asahina und J. Murayama *Arch. Pharm. Berl.* **252**, 448 (1914).
[10] E. Vongerichten *Ber. Dtsch. Chem. Ges.* **34**, 775 (1901).
[11] E. Rap *Gaz. Chim. Ital.* **25**, 288 (1895).
[12] R. Stoermer, C. W. Chydenius und E. Schinn *Ber. Dtsch. Chem. Ges.* **57**, 79 (1924).

Furyl-2-methyl-keton[13] aus Furan, bzw. α-Methyl-furan mit Propionsäureanhydrid, bzw. Essigsäureanhydrid und Phosphorsäure.

Zur Konfigurationsbestimmung der Furylketoxime versuchten wir zunächst die Beckmann'sche Umlagerung anzuwenden. Diese Methode führte—wie schon erwähnt— bei einigen Furyl-aryl-ketoximen zum Ziele, jedoch versagte sie bei den Furyl-alkyl-ketoximen ganz allgemein. Die letzteren blieben nämlich unter milderen Reaktionsbedingungen unverändert, oder aber verharzten unter dem Einfluss von kräftiger wirkenden Mitteln. Dieses unterschiedliche Verhalten des beiden Typs lässt sich wohl auf die grössere Elektronendichte und daher auf grössere Wanderungsbereitschaft der Aryl—gegenüber den Alkyl-Gruppen zurückführen.

Die Umlagerung der einheitlichen Ketoxime mit ätherischer Salzsäure lieferte schliesslich entscheidende Anhaltspunkte für die Konfiguration. Brady und Goldstein[14] haben nämlich auf diese Weise das *syn*-Furfuroloxim (ein *anti*-Furyl-oxim) ins *anti*-Furfuroloxim (ein *syn*-Furyl-oxim) umgewandelt.

Die Konfiguration der beiden Furfuroloxime steht auf Grund von Eliminationsreaktionen fest. Die Umwandlung verlauft fast quantitativ und lässt sich in der entgegengesetzten Richtung nicht durchführen. Das *syn*-Furyl-oxim ist also in ätherischer Salzsäure wesentlich stabiler, als das *anti*-Furyl-oxim. Es kann daher angenommen werden, dass die Richtung der Umlagerung auch in der von uns hergestellten α-Furylketoxim-Reihe dieselbe ist, es lassen sich also nur die *anti*-Furyl-ketoxime in die *syn*-Furyl-ketoxime umlagern, aber nicht umgekehrt.

Im Laufe unserer diesbezüglichen Versuche konnten wir tatsächlich feststellen, dass von den Stereoisomerenpaaren immer nur das eine in das andere Isomere überführbar war. Auf Grund dieser Experimente konnten wir die von uns hergestellten Furyl-ketoximen in zwei Gruppen ordnen, von denen der nicht umlagerbaren die *anti*-Furyl-Konfiguration zugeteilt wurde. Die so abgeleiteten Konfigurationen stehen mit dem Ergebnis der Beckmann'schen Umlagerung von (IV) und (VI) in Einklang, diesen Ketoximen kommt nämlich nach beiden Methoden die *syn*-Konfiguration zu. Die Tabelle 2 zeigt die Konfiguration und Schmelzpunkte der *syn, anti*-isomeren Furylketoxime, bzw. die Schmelzpunkte ihrer Acetate, Benzoate und Tosylate. Während die Acetate und Benzoate verhältnismässig stabil sind, zersetzen sich die Tosylate, besonders die der *anti*-Oxime schnell schon beim Stehen in Exsiccator. Wie aus den Tabellen 1 und 2 ersichtlich, waren die in der Literatur beschriebenen Oxime (III), (IV) und (VI) keine einheitliche Substanzen und somit stellen *syn*-I, *anti*-II, *syn*- und *anti*-(III,) *syn*- und *anti*-(IV,) *syn*-V,) *syn*- und *anti*-(VI) neue Verbindungen dar.

Die Herstellung der aufgezählten Ketoxime ermöglichte erstemals einen systematischen spektroskopischen Vergleich von *syn, anti*-Ketoximpaaren. Die Abb. 1–7 stellen die UV-Spektren der *syn- anti*-Furfurol-oxime und Furyl-ketoxime in Äthanol dar. Im Falle der Furfuroloxime (Abb. 1) und der einfacheren Furyl-ketoxime (Abb. 2–4) zeigt sich erwartungsgemäss[15] bei 270 mμ ein einzieges Maximum. Die Furyl-2-phenyl-ketoxime weisen zwei Maxima auf (Abb. 5), während die Spektren der Benzofuran-Derivate (Abb. 6–7) etwas komplizierter sind. Wie aus den Abb.

[13] H. D. Hartough und A. V. Kosak *J. Amer. Chem. Soc.* **69**, 3093 (1947).
[14] O. L. Brady und R. F. Goldstein *J. Chem. Soc.* 1923 (1926).
[15] K. W. Hausser, R. Kuhn, A. Smakula und A. Deutsch *Z. Phys. Chem.* B **29**, 378 (1935); G. B. Bonino und R. Manzoni-Ansidei *Z. Phys. Chem.* B **25**, 327 (1934).

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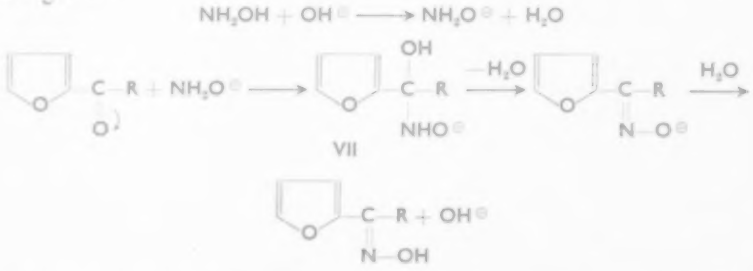
TABELLE 2

Ketoxim	Schmp.	Acetat Schmp.	Benzoat Schmp.	Tosylat Schmp.
syn-Furyl-2-methyl-	–	75°	84°	88°
anti-Furyl-2-methyl-	104°	96°	97–98°	80°
syn-Furyl-2-äthyl-	77–78°	Öl	63°	68°
anti-Furyl-2-äethyl-	73°	94°	93°	70–71°
syn-5-Methyl-furyl-2-methyl-	109°	94°	95°	112°
anti-5-Methyl-furyl-2-methyl-	83°	66°	86°	72°
syn-Furyl-2-phenyl-	149°	68°	99°	118°
anti-Furyl-2-phenyl-	161°	109–110°	144°	84°
syn-Benzofuryl-2-methyl-	161°	77°	90°	140°
anti-Benzofuryl-2-methyl-	154–155°	95–96°	135–136°	100–102°
syn-Benzofuryl-2-phenyl-	145°	81°	120°	112°
anti-Benzofuryl-2-phenyl-	156°	146°	152°	116–118°

1–5 ersichtlich ist gibt es unter den *syn*, *anti*-Isomeren in der Wellenlänge einen kleinen, in der Intensität einen grösseren Unterschied, und zwar absorbieren die *syn*-Furyl-Derivate bei etwas kürzerer Wellenlänge und haben eine grössere Extinktion als die *anti*-Furyl-Derivate. Da die Konfiguration der Furfurol-oxime ausser Zweifel steht, wird die von uns chemisch abgeleitete Konfiguration der Furyl-ketoxime auch spektroskopisch bestätigt. Die theroetische Deutung der Extinktionskurven 1–7 wird von Herrn I. Trummer an anderer Stelle mitgeteilt.

Es wurde beobachtet, dass sich bei Herstellung von Furylketoximen in alkalischem Medium entweder ausschliesslich, oder überwiegend das *anti*-Furyl-derivat bildet, während in saurem, oder neutralem Medium das Gemisch der beiden Isomeren entsteht (z.B. im Falle des Furyl-2-methyl- und Furyl-2-äthyl-ketoxims. Die Erscheinung kann elektrostatisch erklärt werden, wenn man den von Ingold, bzw. Sidgwick vorgeschlagenen Mechanismus für die Bildung der Oxime in alkalischem Medium zu Grunde legt:[16,17]



Das negativ geladene Sauerstoffatom im Anion (VII) ist bestrebt, sich von dem elektronenreichen Furanring möglichst entfernt, in *anti*-Furyl-Position zu drehen.

[16] C. K. Ingold *Structure and Mechanism in Organic Chemistry;* S.687–688. Cornell University Press (1953).
[17] T. W. J. Taylor and W. Baker *Organic Chemistry of Nitrogen* (Ed. Sidgwick) Oxford, S.169–193. (1949).

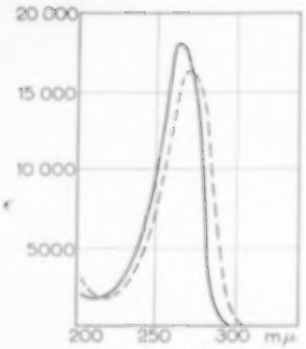


Abb. 1
Furfural-oxime

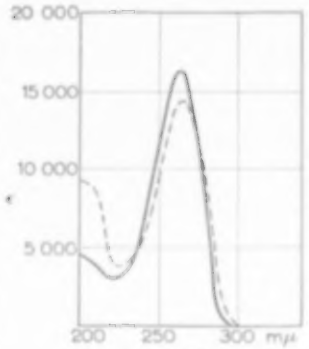


Abb. 2
Furyl-2-methyl-ketoxime

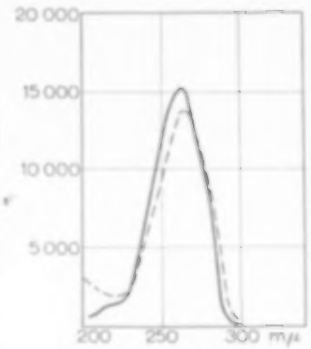


Abb. 3
Furyl-2-aethyl-ketoxime

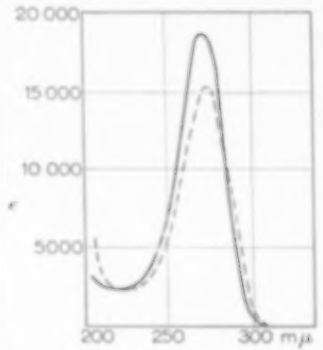


Abb. 4
5-Methyl-furyl-2-methyl-ketoxime

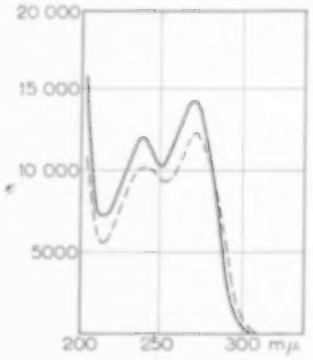


Abb. 5
Furyl-2-phenyl-ketoxime

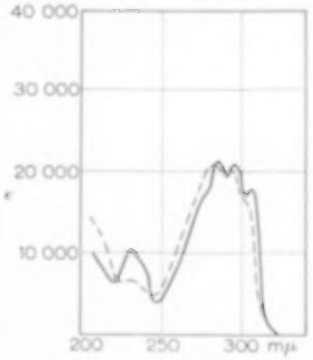


Abb. 6
Benzofuryl-2-methyl-ketoxime

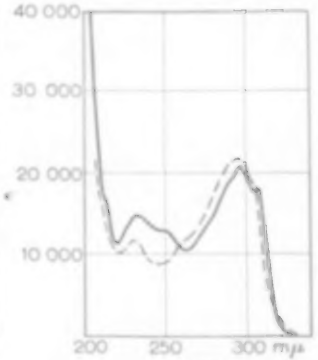
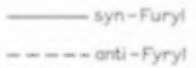


Abb. 7
Benzofuryl-2-phenyl-ketoxime



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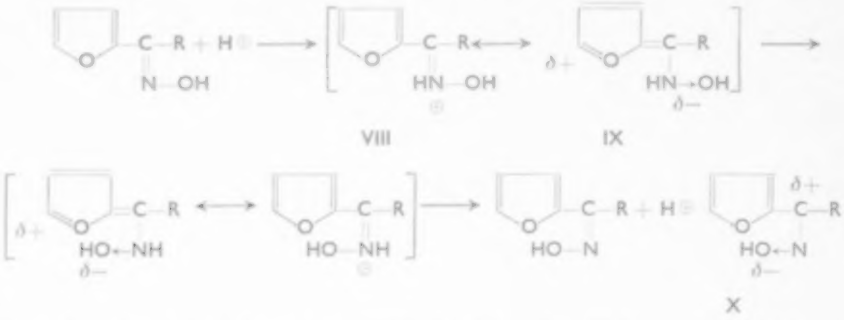
Die von uns für die Umlagerung von Furyl-ketoximen benutzte Methode wurde bisher für Ketoxime nur vereinzelt angewendet. Wir nehmen an, dass sie bei ähnlichen Verbindungstypen nicht nur für die Gewinnung von einheitlichen Ketoximen, sondern auch zur Bestimmung ihrer Konfigurationen allgemein nützlich sein kann. Die Umlagerung kann unter anderen Reaktionsbedingungen auch in der entgegengesetzten Richtung vollgebracht werden. Wenn man z.B. *syn*-Furyl-2-methyl-ketoxim in verdünnter wässriger Schwefelsäure löst und nach einiger Zeit die Lösung neutralisiert, dann kristallisiert das zunächst ölig ausgefallene Oxim nach längerem Stehen in Form des *anti*-Furyl-2-methyl-ketoxims aus. Offenbar ist das Oxim in neutralem wässrigem Medium in der *anti*-Form stabiler, als in der *syn*-Form.

Der Mechanismus der Umlagerung in ätherischer Salzsäure kann im Sinne der folgenden Formeln ebenfalls durch elektrostatische Kräfte gedeutet werden:



VIII IX

X

Der Furanring des Immoniumsalzes (VIII) bewirkt eine Elektronenverschiebung in der Richtung der Oximgruppe und das negativ gewordene Oximsauerstoffatom der mesomeren Verbindung (IX) dreht sich in die Nähe des positiven Furanringes in *cis*-Furyl-Stellung.

Die Rückverwandlung beim Neutralisieren der verdünnten Schwefelsäurelösung könnte über Zwischenstufen wie (VII), oder die "aufgerichtete" Formel (X) erfolgen.

Hauser und Hoffenberg[18] haben zuerst versucht, ähnliche Umlagerungen in der Benzaldoxim-Reihe durch die durch Elektronenverschiebung bedingte freie Drehbarkeit um die C-N-Bindung und durch elektrostatische Kräfte zu erklären.

Wir danken für die Aufnahme der UV-Spektren Herrn I. Trummer und für die Mikroanalysen Frln. Lenke Szabo verbindlichst.

BESCHREIBUNG DER VERSUCHE

Anti-*Furyl-2-methyl-ketoxim* (anti-I). Zu einer Lösung von 100 g (2,5 mol) Natriumhydroxyd in 110 ml Wasser gibt man die Lösung von 86,9 g (1,25 mol) Hydroxylammoniumchlorid in 220 ml Wasser unter Rühren und Kühlung. Dazu tropft man bei 25–30° 110 g Furyl-2-methyl-keton[13] welches sich nach 3-stündigem Rühren vollkommen löst. Nach Zugabe von 200 cm^3 gesättigter Ammoniumchlorid-Lösung wird das ausgefallene Oxim abgesaugt, mit Wasser gewaschen und aus Äthanol umkristallisiert. Ausbeute 80%, Schmp. 104°.

Salzsaures Salz: In eine ätherische Lösung des Ketoxims leitet man trockene Salzsäure. Das ausgefallene Salz wird abfiltriert, mit Äther gewaschen und in Vakuum

[18] Ch. R. Hauser und D. S. Hoffenberg *J. Org. Chem.* **20**, 1491 (1955).

getrocknet. Schmp. 85–90°. Auf die Einwirkung von Wasser liefert das Salz das *anti*-Oxim von Schmpunkte 104° zurück. ($C_6H_8O_2NCl$ (161,6). Ber. HCl, 22,57. Gef. HCl, 21,88).

syn-*Furyl-2-methyl-ketoxim* syn-I. In eine Lösung von 10 g *anti*-Furyl-2-methyl-ketoxim von Schmp. 104° in 250 ml Äther leitet man unter Kühlung trockene Salzsäure bis sich das anfangs ausgefallene Salz wieder löst. Nach Stehen über Nacht wird die Lösung in Vakuum eingetrocknet, der Rückstand mit 2n-Sodalösung behandelt, die Substanz abgesaugt und aus Wasser umkristallisiert. Ausbeute 6,5 g farblose Nadeln. Schmp. 74° ($C_6H_7O_2N$ (126,1). Ber. C, 57,52; H, 5,64; N,11,20. Gef. C, 57,73; H, 5,71; N, 11,46).

Salzsaures Salz; Dargestellt, wie das salzsaure Salz des *anti*-Oxims. Schmp. 128–129° Durch Behandlung mit Wasser liefert das Salz das *syn*-Oxim von Schmp. 74° zurück ($C_6H_8O_2NCl$ (161,6). Ber HCl, 22,57. Gef. HCl, 22,75).

anti-*Furyl-2-methyl-ketoxim* (anti-I) *aus* syn-*Furyl-2-methyl-ketoxim* (syn-I): Man löst 1 g *syn*-Furyl-2-methyl-ketoxim bei 80° in 10 ml 2n-Schwefelsäure und neutralisiert die Lösung nach Stehen über Nacht bei Zimmertemperatur mit 2n-Sodalösung. Das Oxim fällt zunächst ölig aus, es wird aber beim Stehen allmählich fest. Schmp. nach Umkristallisieren aus Äthanol 104°. Ausbeute 0,6 g.

Furyl-2-äthyl-*keton*. In einem mit Kühler, Tropftrichter, Thermometer und Rührer versehenem Kolben werden zu einem auf 40° erwärmten Gemisch von 102 g Furan und 390,4 g (3 mol) Propionsäureanhydrid in 5 Minuten 15 cm³ 85%-ige Phosphorsäure gegeben. Das Reaktionsgemisch wird noch 1 Stunde bei 60–65° gerührt. Nach Abkühlen neutralisiert man das Gemisch mit 600 cm³. 50%-iger Kalilauge und schüttelt es mit Äther mehrmals aus. Die ätherische Lösung wird dann mit Natriumsulfat getrocknet und der Äther abdestilliert. Die zurückbleibende Flüssigkeit siedet unter 11 mm bei 74–75°. Ausbeute 72%.

anti-*Furyl-2-äthyl-ketoxim* (anti-II). Zu einer Lösung von 50 g (1,25 Mol) Natriumhydroxyd in 150 ml Wasser gibt man unter Rühren und Kühlen die Lösung von 43,5 g (0,625 Mol) Hydroxylammoniumchlorid in 150 ml Wasser. Zu dieser Lösung tropft man bei 25–30° 62,1 g (0,5 Mol) Furyl-2-aethyl-keton, welches sich nach 3 stündigem Rühren löst. Nach Zugabe von 120 ml gesättigter Ammoniumchlorid-Lüsung wird das anfangs ölig ausgefallene Oxim beim Reiben allmählich fest. Es wird abgesaugt und zur Reinigung die noch feuchte Substanz in 180 ml Äthanol gelöst, die Lösung filtriert und bei Eiskühlung bis zur bleibenden Trübung ca. mit 400 ml Wasser versetzt. Die ausgeschiedene Emulsion wird bald kristallin. Man erhält 35 g (56%) reines *anti*-Oxim von Schmp. 73°. Die Mutterlauge liefert nach weiterem Verdünnen mit Wasser noch 23 g Oxim von Schmp. 48–50°, welches durch wiederholte Kristallisation gereinigt werden kann. $C_7H_9O_2N$ (139,15). Ber. C, 60,42; H, 6,52; N, 10,06. Gef. C, 60,59; H, 6,62; N, 10,10).

syn-*Furyl-2-äthyl-ketoxim* (syn-II).* Es wird aus *anti*-II analog dem *syn*-Furyl-2-methyl-ketoxim durch ätherische Salzsäure hergestellt. Das Rohprodukt wird aus wässrigem Alkohol umkristallisiert. Ausbeute 83%. Schmp. 77–78°. Die Substanz erwies sich auf Grund des Mischschmp. mit dem auf anderen Wege hergestellten Oxim als identisch.

5-*Methyl-furyl-2-methyl-keton*. Die Substanz wird aus 205,3 g α-Methyl-furan, 510 g Essigsäureanhydrid und 25 g 85%-iger Phosphorsäure analog dem Furyl-2-äthylketons hergestellt. Siedepunkt 78–80°, 12 mm. Ausbeute 38%.

anti-5-*Methyl-furyl-2-methyl-ketoxim* (anti-III). Eine Lösung von 115 g 5-Methyl-furyl-2-methylketon in 650 ml Äthanol wird mit der Lösung von 77,6 g Hydroxylammoniumchlorid und 95,4 g wasserfreiem Natriumacetat in 240 ml Wasser gemischt. Nach 16 Stunden wurden 400–450 ml Alkohol in Vakuum abdestilliert und der Rückstand mit 1000 ml Wasser verdünnt. Beim Kühlen mit Eis scheiden sich farblose Kristalle (117 g, 91%) aus. Nach Umkristallisieren aus 400 ml Benzin erhält man 70 g Oxim vom Schmp. 80–82°. Nochmalige Umkristallisation aus 100 ml Benzin liefert 66 g reines Oxim vom Schmp 83°. Die Mutterlaugen enthalten das Gemisch der beiden Isomeren. ($C_7H_9O_2N$ (139,1) Ber. C, 60,42; H, 6,52; N, 10,06. Gef. C, 60,61; H, 6,70; N, 9,98).

syn-5-*Methyl-furyl-2-methyl-ketoxim* (syn-III). Das aus den Benzin-Mutterlaugen von *anti*-(III) durch Eindampfen gewonnene Gemisch wird, wie bei der Darstellung des *syn*-(I) beschrieben, mit ätherischer Salzsäure behandelt. Das Rohprodukt wird aus Benzin umkristallisiert. Ausbeute 88% Schmp. 109° ($C_7H_9O_2N$ (139,1). Ber C, 60,42; H, 6,52; N, 10,06. Gef. C, 60,46; H, 6,48; N, 10,10.).

anti-*Furyl-2-phenyl-ketoxim* (anti-IV). Ein Gemisch von 94,6 g Furyl-2-phenylketon,[8] 46 g Hydroxylammoniumchlorid und 56,2 g wasserfreiem Natriumacetat wird in 550 ml abs. Äthanol 1 Stunde rückfliessend gekocht. Das Reaktionsgemisch wird heiss filtriert und mit 140 ml abs. Äthanol nachgewaschen. Nach 2 tägigem Stehen werden die würfeligen Kristalle abgesaugt und aus Äthylacetat umkristallisiert. Ausbeute 23,5 g (23%). Schmp. 161°. Das durch Einengen der alkoholischen Mutterlauge erhaltene Isomerengemisch (72 g, Schmp. 132–135°) konnte durch Kristallisation nicht mehr getrennt werden, es wurde zur Bereitung des *syn*-Isomeres verwendet, oder durch Kochen mit 10% iger Salzsäure in das Keton zurückverwandelt. ($C_{11}H_9O_2N$ (187,2). Ber. C, 70,57; H, 4,85; N, 7,48. Gef. C, 70,63; H, 4,55; N, 7,65).

syn-*Furyl-2-phenyl-ketoxim* (syn-IV). Durch Behandlung des aus der alkoholischen Mutterlauge von *anti*-(IV) erhältlichen Gemisches, oder des reinen *anti*-(IV) mit ätherischer Salzsäure. Das Rohprodukt kristallisiert man aus verdünntem Äthanol um. Ausbeute 96%. Schmp. 149° ($C_{11}H_9O_2N$ (187,2). Ber. C, 70,57; H, 4,85; N, 7,48; Gef. C, 70, 78; H, 4,76, N, 7,53).

syn-*Benzofuryl-2-methyl-ketoxim* (syn-V). Aus dem *anti*-(V) vom Schmp. 154–155°[2,10] durch Umlagerung mit ätherischer Salzsäure. Das Rohprodukt kristallisiert man aus wässrigem Alkohol um. Ausbeute 84% Schmp. 161°. ($C_{10}H_9O_2N$ (175,2). Ber. C, 68,56; H, 5,17; N, 8,0. Gef. C. 68,24; H, 5,01; N, 8,13).

Benzofuryl-2-phenyl-ketoxim, Gemisch der beiden Isomeren (VI). Zu einer heissen Lösung von 111 g (0,5 Mol) Benzofuryl-2-phenyl-keton[11,12] in 2 Liter Methanol gibt man die Lösung von 69,5 g Hydroxyammoniumchlorid (1 Mol) in 120 cm³ Wasser und eine Lösung von 100 g (2,5 mol.) Natriumhydroxyd in 120 ml Wasser. Das Reaktionsgemisch wird 20 Minuten gekocht, dann eingeengt, der Rückstand mit 750 ml Wasser und 250 cm³ gesattigter Ammoniumchlorid-Lösung versetzt. Das ausgeschiedene Oxim wird zur Reinigung in wenig Äthanol gelöst, filtriert, und mit Wasser gefällt. Ausbeute 111 g (94%). Schmp, 130–133°.

anti-*Benzofuryl-2-phenyl-ketoxim-acetat*. 53,4 g vom Oximgemisch (VI) wird mit 267 cm³ Essigsaureanhydrid geschüttelt, bis Lösung erfolgt. Aus dieser Lösung scheiden sich nach 1-tägigem Stehen würfelige Kristalle aus. Durch Absaugen gewinnt man 10,6 g *anti*-Ketoxim-acetat von Schmp. 146°. Die mit der 2-fachen Menge Eiswasser versetzte Essigsaureanhydrid-Lösung wird mit festem Soda neutralisiert bis

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die anfangs ölige Ausscheidung fest wird. Man erhält 50 g Substanz, welche aus der 4-fachen Menge Alkohol einigemal umgelöst wird, bis der Schmp. 135–140° erreicht. Nach Umkristallisieren aus Äthylacetat erhält man 18,9 g reines *anti*-Ketoxim-acetat von Schmp. 146°. Gesamtausbeute 29,5 g (47%). ($C_{17}H_{13}O_3N$ (279,3). Ber. N, 5,02. Gef. N, 5,23).

anti-*Benzofuryl-2-phenyl-ketoxim* (anti-VI). Man erhitzt eine Suspension von 20 g anti-Benzofuryl-2-phenyl-ketoxim-acetat in 200 ml 2*n*-Natronlauge beinahe zum Sieden, bis sich alles löst. Nach Abkühlen gibt man zur Lösung 200 cm³ Wasser und unter Rühren 85 cm³ gesättigte Ammoniumchlorid-Lösung. Das ausgeschiedene Oxim wird abgesaugt, mit Wasser gewaschen und in Vakuum getrocknet. Dieses Rohprodukt (16,9 g) wird in wenig Toluol unter gelindem Erwärmen gelöst und die Lösung filtriert. Auf die Zugabe von Petroläther fallen 11,7 g Oxim vom Schmp. 140–153° aus. Die Lösung des rohen Oxims in wenig heissem Aethanol wird bis zur beginnednen Trübung mit heissem Wasser versetzt. Beim Abkühlen scheiden sich 10 g (59%) farblose Nadeln von Schmp. 156° aus ($C_{15}H_{11}O_2N$ (237,2). Ber. C, 75,93; H, 4,67; N,5,91. Gef. C, 75,99; H, 4,65; N, 5,88).

syn-*Benzofuryl-2-phenyl-ketoxim* (syn-VI). Aus dem Gemisch (VI), oder aus reinem *anti*-(VI) durch Umlagerung mit ätherischer Salzsäure. Das Rohprodukt wird aus wässrigem Methanol umkristallisiert. Schmp. 145°. $C_{15}H_{11}O_2N$ (237,2). Ber. C, 75,93; H, 4,67; N, 5,91. Gef. C, 76,01; H, 4,87; N,5,91).

Allgemeine Methode zur Darstellung von Acylderivaten der Oxime. Zur Herstellun der Acetate werden die Oxime mit der 10-fachen Menge Essigsäureanhydrid geschüttelt bis sich das Oxim löst. Nach 3-stündigem Stehen giesst man das Reaktionsgemisch in Eiswasser, stumpft die Säure mit Soda ab und saugt das auskristallisierte Acetat ab. Zur Herstellung der Benzoate und Tosylate werden die Oxime (0.01 Mol) in 10 ml Pyridin mit der äquivalenten Menge Benzoylchlorid, bzw. Tosylchlorid bei −5°–10° acyliert. Nach 1 stündigem Stehen bei 0° wird das Acylierungsgemisch auf Eiswasser gegossen und das abgesaugte, mit Wasser gewaschene Produkt im Vakuum über Schwefelsäure und Kalilauge getrocknet. Die leicht zersetzlichen *anti*-Tosylate müssen mit besonderer Sorgfalt behandelt werden.

syn-*Furyl-2-methyl-ketoxim-acetat.* Umkristallisieren aus Wasser. Schmp. 75° ($C_8H_9O_3N$ (167,2). Ber. C, 57,48; H, 5,43; N, 8,38. Gef. C, 57,58; H, 5,47; N, 8,58).

syn-*Furyl-2-methyl-ketoxim-benzoat.* Aus Benzin, Schmp. 84° ($C_{13}H_{11}O_3N$ (229,2) Ber. C, 68,11; H, 4,84; N, 6,11. Gef. C, 68,15; H, 5,13; N, 6,43).

syn-*Furyl-2-methyl-ketoxim-tosylat.* Aus wenig Benzol mit Benzin. Schmp. 88° ($C_{13}H_{13}O_4NS$ (279,3). Ber. C, 55,90; H, 4,69; N, 5,02; S, 11,48. Gef. C, 56,16; H, 4,73; N, 5,05; S, 11,36).

anti-*Furyl-2-äthyl-ketoxim-acetat.* Umkristallisiert aus Benzin. Schmp. 94° ($C_9H_{11}O_3N$ (181,2). Ber. C, 59,66; H, 6,12; N, 7,73. Gef. C, 59,65; H, 6,39; N, 7,64).

anti-*Furyl-2-äthyl-ketoxim-benzoat.* Farblose Blätter aus Benzin. Schmp. 93° ($C_{14}H_{13}O_3N$ (243,2). Ber. C, 69,12; H, 5,59; N, 5,76. Gef. C, 69,26; H, 5,58; N, 5,63).

anti-*Furyl-2-äthyl-ketoxim-tosylat.* Aus wenig Benzol mit Benzin. Schmp. 70–71° unter Zersetzung. Die Substanz zersetzt sich beim Stehen. Es kam vor, dass sich das Rohprodukt nach Abgiessen des Wassers in einigen Minuten mit explosionsartiger Heftigkeit unter Hinterlassung von schwarzem Teer zersetzte ($C_{14}H_{15}O_4NS$ (293,3). Ber. N, 4.78. Gef. N, 4,99).

syn-*Furyl-2-äthyl-ketoxim-acetat*. Öl, es konnte nicht in kristallisiertem Zustand erhalten werden.

syn-*Furyl-2-äthyl-ketoxim-benzoat*. Umkristallisiert aus Benzin. Schmp. 63° ($C_{14}H_{13}O_3N$ (243,2). Ber. N, 5,76. Gef. N, 5,62).

anti-5-*Methyl-furyl-2-methyl-ketoxim-acetat*. Aus Benzin. Schmp. 66° ($C_9H_{11}O_3N$ (181,2). Ber. N, 7,73. Gef. N, 7,72).

anti-5-*Methyl-furyl-2-methyl-ketoxim-benzoat*. Farblose Nadeln aus Benzin. Schmp. 86° ($C_{14}H_{13}O_3N$ (243,2). Ber. N, 5,76. Gef. N, 5,79).

anti-5-*Methyl-furyl-2-methyl-ketoxim-tosylat*. Farblose Kristalle aus Benzol mit Benzin. Schmp. 72° unter Zersetzung ($C_{14}H_{15}O_4NS$ (293,26). Ber. N, 4,77. Gef. N, 4,85).

syn-5-*Methyl-furyl-2-methyl-ketoxim-acetat*. Aus Benzin, Schmp. 94° ($C_9H_{11}O_3N$ (181,2). Ber. N, 7,73. Gef. N, 7,77).

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syn-5-*Methyl-furyl-2-methyl-ketoxim-benzoat*. Farblose Nadeln aus Benzin, Schmp. 95° ($C_{14}H_{13}O_3N$ (243.2). Ber. N, 5,76. Gef. N, 5,58).

anti-*Furyl-2-phenyl-ketoxim-acetat*. Farblose Nadeln aus Benzin. Schmp. 109–110° ($C_{13}H_{11}O_3N$ (229,2). Ber. N, 6,11. Gef. N, 6,33).

anti-*Furyl-2-phenyl-ketoxim-benzoat*. Nadeln aus Aethylacetat. Schmp. 144° ($C_{18}H_{13}O_3N$ (291,3). Ber. N, 4,81. Gef. N, 5,08).

anti-*Furyl-2-phenyl-ketoxim-tosylat*. Aus wenig Aceton mit Wasser. Schmp. 84° ($C_{18}H_{15}O_4NS$ (341,4). Ber. N, 4,10. Gef. N, 4,20).

syn-*Furyl-2-phenyl-ketoxim-acetat*. Aus Benzin. Schmp. 68° ($C_{13}H_{11}O_3N$ (229,2). Ber. N, 6,11. Gef. 6,15).

syn-*Furyl-2-phenyl-ketoxim-benzoat*. Farblose Nadeln aus Aethanol. Schmp. 99–100° ($C_{18}H_{13}O_3N$ (291,3). Ber. N, 4,81. Gef. 4,81).

anti-*Benzofuryl-2-methyl-ketoxim-acetat*. Aus Benzin. Schmp. 95–96° ($C_{12}H_{11}O_3N$ (193,2). Ber. N, 6,45. Gef. N, 6,54).

anti-*Benzofuryl-2-methyl-ketoxim-benzoat*. Aus Alkohol. Schmp. 135–136° ($C_{17}H_{13}O_3N$ (279,3). Ber. N, 5,02. Gef. N, 5,05).

syn-*Benzofuryl-2-methyl-ketoxim-acetat*. Aus Benzin. Schmp. 77° ($C_{12}H_{11}O_3N$ (217,2). Ber. N, 6,45. Gef. N, 6,55).

syn-*Benzofuryl-2-methyl-ketoxim-benzoat*. Aus Benzin. Schmp. 90° ($C_{17}H_{13}O_3N$ (279,3). Ber. N, 5,02. Gef. N, 5,37).

syn-*Benzofuryl-2-methyl-ketoxim-tosylat:* Aus Aceton mit Wasser. Schmp. 140° ($C_{17}H_{15}O_4NS$ (329,4). Ber. N, 4,25; S, 9,74. Gef. N, 4,26; S, 9,85).

anti-*Benzofuryl-2-phenyl-ketoxim-benzoat*. Aus Alkohol. Schmp. 152° ($C_{22}H_{15}O_3N$ (341,3). Ber. N, 4,13. Gef. N, 4,30).

anti-*Benzofuryl-2-phenyl-ketoxim-tosylat*. Es wurde von der allgemeinen Methode etwas abweichend dargestellt. Zur Lösung von 10,2 g Ketoximin 20 ml Pyridin gibt man allmählich 9 g Tosylchlorid bei −5°– −10°. Man lässt das Reaktionsgemisch 1 Stunde bei 0° stehen und giesst es dann in 150 ml Eiswasser. Falls das Produkt beim Reiben und Kühlen nicht fest wird, giesst man das Wasser ab und verrührt das Öl mit wenig Aceton. Hierauf löst sich das Öl teilweise auf und der Rest wird kristallin. Beim Verdünnen mit Wasser fällt auch der gelöste Teil kristallin aus. Die Substanz wird abgesaugt, mit 2 n-Salzsäure und mit Wasser gewaschen. Ausbeute 15,25 g. Zur Reinigung wird das Produkt zuerst aus Aceton mit Eiswasser, dann aus wenig Benzol mit Petroläther umgelöst. Schmp. 116–118° ($C_{22}H_{17}O_4NS$ (391,4). Ber. N, 3,58.Gef. N, 3,84).

syn-*Benzofuryl-2-phenyl-ketoxim-acetat*. Aus Alkohol, Schmp. 81° ($C_{16}H_{13}O_3N$ (267,3). Ber. N, 5,02. Gef. N, 4,97).

syn-*Benzofuryl-2-phenyl-ketoxim-benzoat*. Schmp. nach Umkristallisieren aus Äthanol 120° ($C_{22}H_{15}O_3N$ (341,3). Ber. N, 4,13. Gef. N, 4,08).

syn-*Benzofuryl-2-phenyl-ketoxim-tosylat*. Das Rohprodukt wird zuerst aus Aceton mit Wasser, dann aus Benzol mit Petroläther umgelöst. Schmp. 112° ($C_{22}H_{17}O_4$ NS (391,4). Ber. N, 3,58. Gef. N, 3,83).

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UNTERSUCHUNGEN ÜBER FURAN-VERBINDUNGEN—VI

STEREOSPEZIFISCHE RINGÖFFNUNGSREAKTIONEN IN DER FURAN-REIHE*

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Zusammenfassung—Die Umwandlungen von Furyl-2-ketoxim-*p*-toluolsulfonaten mit Alkoholen sind von ihren Konfigurationen abhängig. Die Tosylate der *syn*-Furyl-2-alkyl-ketoxime bleiben unverändert, die *syn*-Furyl-2-aryl-ketoxim-tosylate erleiden unter Bildung von Furan-2-carbonsäure-aniliden eine Beckmann'sche Umlagerung, während die entsprechenden *anti*-Furyl-Derivate im allgemeinen unter Öffnung des Furan-Ringes die Acetale von reaktionsfähigen ungesättigten Trioxo-Verbindungen liefern. Eine Ausnahme bildet das Tosylat des *anti*- 5-Methyl-furyl-2-methyl-ketoxims, aus dem in Folge von Beckmann'scher Umlagerung Lävulinsäureester entsteht. Es wird versucht, die Stereospezifität der Reaktionen, so wie das anomale Verhalten des *anti*-5-Methyl-Derivates zu deuten.

Abstract—The conversions of furyl-2-ketoxime *p*-toluenesulphonates with alcohols are dependent on their configurations. Tosylates of the *syn*-furyl-2-alkyl-ketoximes remain unchanged, but *syn*-furyl-2-aryl-ketoxime tosylates undergo a Beckmann rearrangement to yield furan-2-carboxylic acid anilides, whereas the corresponding *anti*-furyl derivatives afford in general acetales of reactive unsaturated trioxo-compounds with opening of the furan ring. An exception to this rule is the tosylate of anti-5-methyl-furyl-2-methyl-ketoxime from which levulinic acid arises in consequence of a Beckmann rearrangement. An attempt is made to elucidate the stereospecifity of the reactions as well the anomalous behaviour of the *anti*-5-methyl derivatives.

Es WURDE unlängst gezeigt,[1] dass das Tosylat des Furyl-2-methyl-ketoxims (I) in wasserhaltigem Äthanol oder Methanol schon bei Zimmertemperatur eine eigenartige Ringöffnung erleidet, wobei in guter Ausbeute Ammonium-*p*-toluolsulfonat und das Diäthyl-, bzw. Dimethyl-acetal des eis-Hexen-2-dion-4, 5-als (II) entsteht. Die Umwandlung erfolgt nach der folgenden Summengleichung(1):

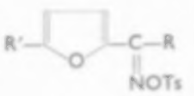
(I) (II)

Diese ziemlich empfindliche, ungesättigte Trioxo-Verbindung (II) verdient ein gewisses Interesse nicht nur wegen ihrer merkwürdigen Bildungsweise, sondern auch deshalb, weil sie zur Synthese von verschiedenen Körperklassen brauchbar ist. Es sei auf die Bildung von Brenzkatechin, Tropan- und Pyridazin-Derivaten verwiesen.

* Im Auszug vorgetragen auf der Tagung der Chemischen Gesellschaft in der DDR am 22 Oktober 1955, zu Leipzig.

[1] L. Vargha, J. Ramonczai und P. Bite *J. Amer. Chem. Soc.* **70**, 371 (1948).

Die erwähnten Befunde veranlassten uns, die Reaktion auch auf die Tosylate von anderen Furyl-2-ketoximen auszudehnen.[2] Es wurde daher die Reaktion der Tosylate des Furyl-2-äthyl-(III), Furyl-2-hydroxymethyl-(IV), 5-Methyl-furyl-2-methyl-(V), Furyl-2-phenyl-(VI) und des Furyl-2-(*p*-methoxy-phenyl)-ketoxims (VII) mit Alkohol untersucht.



(III) $R = C_2H_5$, $R' = H$
(IV) $R = CH_2OH$, $R' = H$
(V) $R = R' = CH_3$
(VI) $R = C_6H_5$, $R' = H$
(VII) $R = p\text{—}CH_3O\text{-}C_6H_4$, $R' = H$

Es stellte sich jedoch heraus, dass mit Ausnahme von (IV) entweder keine Reaktion erfolgte, oder wenn R eine aromatische Gruppe war (VI, VII), unter Bildung des entsprechenden Anilids der Furan-2-carbonsäure eine Beckmann'sche Umlagerung stattfand.

Das unerwartete Ergebnis dieser Versuche erweckte in uns die Vermutung, dass der verlauf der Reaktionen vielleicht von der Konfiguration der Oxime abhängig ist. Um die Richtigkeit dieser Annahme prüfen zu können, haben wir einige bisher unbekannten stereoisomeren Oximpaare hergestellt und ihre Konfiguration bestimmt.[3] In der vorliegenden Mitteilung wird über die Reaktionen der Tosylate (I), (III), (V) und (VI) mit Alkohol berichtet.

Unsere diesbezügliche Versuche bestätigten durchaus die Vermutung, dass die Ringöffnungsreaktionen stereospezifisch verlaufen. Es stellte sich ganz allgemein heraus, dass lediglich die Tosylate der *anti*-Furyl-ketoxime mit Alkoholen unter Bildung von ungesättigten Trioxo-Verbindungen und toluolsulfonsaurem Ammonium reagieren. Die Tosylate der *syn*-Alkyl-ketoxime blieben unter den gewöhnlichen milden Reaktionsbedingungen unverändert, oder zersetzten sich in der Wärme unter Bildung von Ammonium-*p*-toluolsulfonat, während das *syn*-Aryl-ketoximtosylat (VI), wie schon früher festgestellt[2], eine Beckmann'sche Umlagerung erlitt. Die Bildung von Ammoniumtosylat aus den *syn*-Alkyl-ketoxim-tosylaten lässt sich durch langsame Umlagerung ins *anti*-Derivat erklären, die sich bildende empfindliche Trioxo-verbindung geht jedoch in der Wärme zugrunde.

Aus *anti*-(III) und *anti*-(V) entstanden nach Gleichung (1) das Diäthyl-acetal des 4,5-Dioxo-2-heptenals (VIII), bzw. das Diäthyl-acetal des 5-Phenyl-4,5-dioxo-2-pentenals (IX):

$CH_3\text{-}CH_2\text{-}CO\text{-}CO\text{-}CH{:}CH\text{-}CH(OC_2H_5)_2$ (VIII) $C_6H_5\text{-}CO\text{-}CO\text{-}CH{:}CH\text{-}CH(OC_2H_5)_2$ (IX)

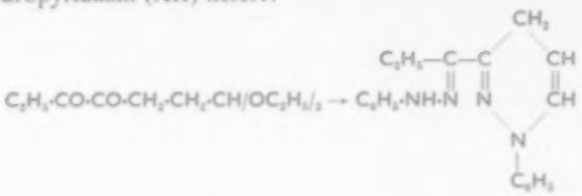
Die Konstitutionsermittlung von (VIII) und (IX) ruht auf den folgenden experimentellen Tatsachen. Substanz (VIII) bildet mit Hydroxylammoniumchlorid in Analogie zu (II)[1] unter Hydrolyse der Acetalbildung ein Oxim (X):

$CH_3\text{-}CH_2\text{-}CO\text{-}CO\text{-}CH{:}CH{:}CH{:}NOH$
(X)

Substanz (VIII) nimmt bei der Hydrierung leicht 1 Mol Wasserstoff auf unter Bildung des gesättigten Heptan-4,5-dion-al-1-diäthylacetals (XI), welches mit Phenylhydrazin,

[1] L. Vargha und F. Gönczy *J. Amer. Chem. Soc.* **72**, 2738 (1950).
[2] G. Ocskay und L. Vargha *Tetrahedron* **2**, 140 (1958).

wie eine 1,4-Dioxoverbindung, ein Dihydropyridazin-Derivat, das 1-Phenyl-3-propionyl-1,4-dihydropyridazin (XII) liefert:



(XI) (XII)

Schliesslich wurde die Konstitution von (VIII) bzw. (XI) eindeutig erwiesen durch Überführung von (XI) mit verdünnter Schwefelsäure in 2,3-Dihydroxy-toluol (XIV), welches auch durch sein bisher unbekanntes, gut kristallisierendes Dibenzoyl-Derivat charakterisiert wurde. Die Umwandlung verläuft über die Enol-Form des nicht isolierten Diketo-aldehyds (XIII) nach folgendem Schema:

A

Die Reaktion liefert ein neues Beispiel[1] zur Bildung von Brenzkatechin-Derivaten aus 1,4,5-Trioxo-Verbindungen.

Die Konstitution von (IX) konnte durch oxydativen Abbau ermittelt werden. Substanz (IX) lieferte nämlich mit Wasserstoffperoxyd in Essigsäure unter Hydrolyse der Acetal-Bindung Benzoesäure und Maleinsäure, während dementsprechend das aus (IX) durch Hydrierung erhaltene gesättigte Acetal (5-Phenyl-4,5-dioxo-pentanal-diäthylacetal, XV) unter denselben Bedingungen Benzoesäure und Bernsteinsäure lieferte:

$$(IX) \rightarrow C_6H_5\text{-}CO\text{-}CO\text{-}CH{:}CH\text{-}CHO \rightarrow C_6H_5\text{-}COOH + HOOC\text{-}CH{=}CH\text{-}COOH$$

$$\underset{(XV)}{C_6H_5\text{-}CO\text{-}CO\text{-}CH_2\text{-}CH_2\text{-}CH(OC_2H_5)_2} \rightarrow C_6H_5\text{-}COOH + HOOC\text{-}CH_2\text{-}CH_2\text{-}COOH + 2C_2H_5OH$$

Die Bildung der Maleinsäure beweist gleichzeitig die *cis*-Konfiguration von (IX).

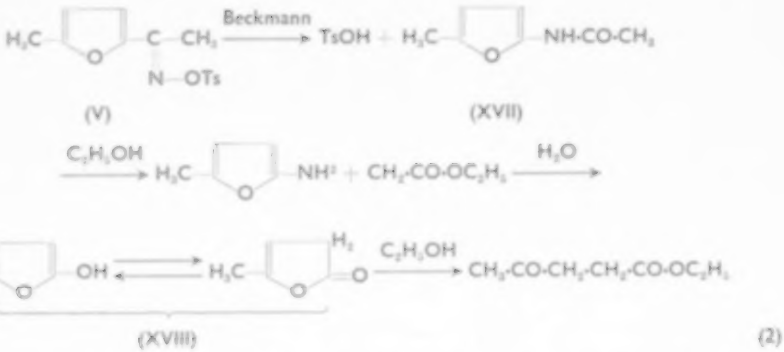
Eine Ausnahme bildet unter den *anti*-Derivaten das Tosylat des 5-Methyl-furyl-2-methyl-ketoxims (V), welches bei der Reaktion mit Äthanol und Methanol nicht das erwartete Trioxo-Derivat (XVI), sondern neben Ammoniumtosylat Lävulinsäure-äthyl-, bzw. -methyl-ester und Essigsäureäthylester, bzw. Essigsäure lieferte.

(XVI)

Die Identität der Lävulinsäureester konnte durch ihre physikalischen Konstanten, Analyse und Vergleich ihrer Semicarbazone mit authentischen Präparaten ermittelt werden.

Die Bildung der Lävulinsäureester lässt sich durch eine Beckmann'sche Umlagerung, unter intermediärer Bildung von 5-Methyl-2-acetylamino-furan (XVII)

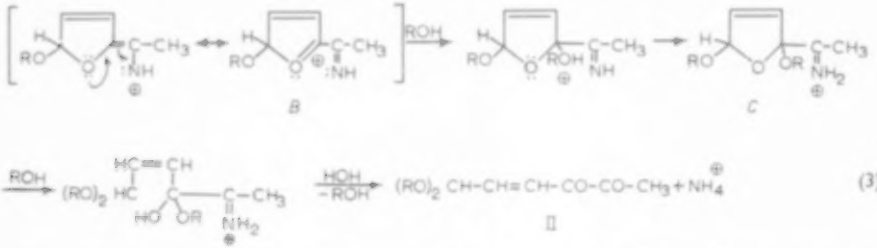
erklären, welches sich nach Schema (2) über das α-Angelicalacton (XVIII) zu Lävulinsäure-ester umsetzt:



(V) (XVII) (XVIII) (2)

Die Bildung der Lävulinsäureester bestätigt einerseits die von uns auf anderem Wege abgeleitete *anti*-Furyl-Konfiguration des 5-Methyl-furyl-2-methyl-ketoxims von Schmp. 83°, andererseits-wie es weiter unten gezeigt wird-verstärkt das scheinbar anomale Verhalten dieses Furan-Derivates die postulierte Regelmässigkeit.

Um den Mechanismus der geschilderten Ringöffnungsreaktionen elektronentheoretisch zu deuten, stellten Dunlop und Peters[4] in ihrem 1953 erschienen Buche "The Furans" die folgende Formelreihe auf, jedoch ohne experimentelle Beweise und natürlich in Unkenntnis unserer neueren Untersuchungen (Schema 3):



(3)

Die erste Phase stellt eine Ionisation dar, womit ein ähnliches Kation entsteht, wie bei der Beckmann'schen Umlagerung angenommen wird. Hierauf erfolgt Anlagerung von Alkohol auf das ausreichend positive mesomere Kation A. Die nächste Phase stellt eine intramolekulare Oxydoreduktion dar, in dem der Stickstoff reduziert, der Kern oxydiert wird. Die Addition von Alkohol und der intramolekulare Oxydations-Reduktions-vorgang wiederholt sich am entstandenen Kation B, und schliesslich erscheint das Endprodukt (II) unter Öffnung des Acetal-Ringes C und Hydrolyse zum Ammonium-ion.

Dieser Reaktionsmechanismus steht mit unseren experimentellen Ergebnissen in Einklang, sie können sogar zur Unterstützung dieses Mechanismus herangezogen werden. Die Vorbedingung der Ringöffnungsreaktion ist nämlich nach Schema 3 das Vorhandensein eines genügend positiv geladenen Kations A, an das die nucleophyle Addition des schwach basischen Alkohols erfolgen kann. Wenn diese Bedingung nicht erfüllt ist, könnte eine Beckmann'sche Umlagerung erwartet werden. Das ist

[4] A. P. Dunlop und F. Peters *The Furans* S. 659, New York (1953).

tatsächlich der Fall bei dem Tosylat des 5-Methyl-furyl-2-methyl-ketoxims (V), dessen elektronenspendende Methyl-Gruppe die positive Ladung des Kations A vermindert.

Auch die Stereospezifität der Ringöffnungsreaktionen kann zur Stützung des geschilderten Mechanismus herangezogen werden. An Stuart-Briegleb-Modellen lässt sich zeigen (Abb. 1 und 2), dass bei den *anti*-Furyl-ketoximen die drei Doppelbindungen, nämlich die Doppelbindungen des Furankerns und der Oximbindung, ohne sterische und elektrostatische Hinderung in eine Ebene gebracht werden können. Demzufolge kann eine vollkommene Konjugation und damit die Verschiebung der Mesomerie in der Richtung des positiven Kations A erfolgen. In diesem Falle ist die Vorbedingung für die Ringöffnungsreaktion erfüllt. Bei den *syn*-Isomeren können die drei Doppelbindungen am Modell nur dann in eine Ebene gebracht werden, wenn das Ringsauerstoffatom und das Oximsauerstoffatom in unmittelbare Nähe zueinander kommen. In Wirklichkeit können also die drei Doppelbindungen infolge elektrostatischer Abstossungskräfte nicht in einer Ebene liegen und deshalb ist bei den *syn*-Isomeren die Vorbedingung für die Ringöffnungsreaktion nicht erfüllt.

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Hepten-2-dion-4,5-al-diäthylacetal-1 (VIII). 55 g *anti*-Furyl-2-äthyl-ketoximtosylat[3] werden in 320 ml 95%-igem Äthanol geschüttelt. Die Substanz geht ca. in 2 Stunden unter Erwärmung in Lösung unter gleichzeitiger Ausscheidung von *p*-toluolsulfonsaurem Ammonium. Die Temperatur hält man während dieser Zeit durch Kühlung zwischen 25–30°. Am anderen Tage wird das ausgeschiedene *p*-toluolsulfonsaure Ammonium abgesaugt, mit wenig Äthanol gewaschen und aus Äthanol umkristallisiert. Ausbeute 61% ($C_7H_{11}O_3NS$ (189,2). Ber. N, 7,40; S, 16,94. Gef. N, 7,46; S, 16,4).

Das rotbraune Filtrat engt man in Vakuum ein, den Rückstand nimmt man in 250 ml Äther und 50 ml Wasser auf und trennt die beiden Schichten. Die wässrige Schicht wird noch dreimal mit je 15 ml Äther ausgeschüttelt, die vereinigten Äther-Lösungen nach Trocknen mit Natriumsulfat eingedampft und der Rückstand in Vakuum destilliert. Man erhält 27,4 g (68%) als hellgelbes Öl. Siedepunkt 80–81° unter 0,7 mm. Die Substanz ist wenig löslich in Wasser, leicht löslich in organischen Lösungsmitteln. Sie reduziert Fehlingsche Lösung und ammoniakalische Silberlösung schon in der Kälte ($C_{11}H_{18}O_4$ (214,2). Ber. C, 61,66; H, 8,47. Gef. C, 61,58; H, 8,57).

Hepten-2-dion-4,5-aldoxim (X). Man schüttelt eine Lösung von 0,6 g Hydroxylammoniumchlorid mit 0,6 g Acetal (VIII) unter gelindem Erwärmen, bis die öligen Tropfen verschwinden und das Oxim auskristallisiert. Man erhält es in farblosen Nadeln von Schmp. 170–171° nach Umlösen aus heissem Wasser. Ausbeute 75% ($C_7H_9O_3N$ (155,1). Ber. C, 54,18; H, 5,85; N, 9,03 Gef. C, 54,44; H, 5,99; N, 9,10).

Heptan-dion-4,5-al-diäthylacetal-1 (XI). 16 g Hepten-2-dion-4,5-al-diäthylacetal (VIII) werden in 80 ml 95%-igem Äthanol in Gegenwart von 3 g Palladium-Kohle (8% Pd) hydriert. Nach Aufnahme von 1 Mol Wasserstoff (ca. 90 Minuten) wird der Katalisator abgesaugt, die Lösung eingedampft und der Rückstand in Vakuum destilliert. Siedepunkt 71–73°, 0,6 mm. Man erhält 13,3 g (82%) einer hellgelben Flüssigkeit $C_{11}H_{20}O_4$ (216,3). Ber. C, 61,09; H, 9,32. Gef. C, 60,95; H, 9,27).

1-*Phenyl-3-propionyl*-1,4-*dihydropyridazin-phenylhydrazon* (XII). 0,5 g Heptandion-4,5-al-diäthylacetal (XI) werden in 5 ml Eisessig mit 1 g Phenylhydrazin 15

Minuten auf dem Wasserbade erhitzt. Der Niederschlag wird nach Abkühlen abgesaugt, mit Wasser und Äthanol gewaschen und aus Chloroform mit Benzin umgelöst. Man erhält 0,35 g einer hellgelben Substanz, welche bis 250° nicht schmilzt $C_{19}H_{20}N_4$ (304,4). Ber. C, 74,96; H, 6,62; N, 18,41. Gef. C, 74,64; H, 6,80; N, 18,42).

2,3-*Dihydroxy-toluol* (XIV) *aus* XI. Eine Lösung von 5,5 g gesättigtem Acetal (XI) in 120 ml 2%-iger Schwefelsäure wird eine Stunde rückfliessend gekocht. Nach Abkühlen schüttelt man die gelb-braune Lösung fünfmal mit je 40 ml Äther aus, dampft die Äther-Lösung nach Trocknen mit Natriumsulfat ein und destilliert den Rückstand in Vakuum. Man erhält bei 99–100° unter 0,5 mm ein viskoses Öl(2,g) aus dem beim Abkühlen mit Eis-Kochsalz farblose, sehr hygroskopische Nadeln ausscheiden. Die Substanz zeigt die Farbreaktionen des 2,3-Dihydroxy-toluols. Ihre wässrige Lösung wird mit Ferrichlorid graugrün, die Farbe schlägt auf Zugabe von Ammoniak in rot um. Sie löst sich in Alkalien mit roter Farbe, die Lösung wird aber durch Oxydation schnell schwarz. Wegen ihres niedrigen Schmelzpunktes (47°) und ungünstiger Löslichkeitsverhältnisse haben wir auf eine vollkommene Reinigung verzichtet.

2,3-*Dibenzoyloxy-toluol*. 0,33 g öliges 2,3-Dihydroxytoluol in 6 ml Pyridin werden mit 0,78 g Benzoylchlorid versetzt, nach 1 Stunde wird in Eiswasser gegossen. Man erhält ein farbloses kristallines Produkt (0,85 g), welches aus Äthanol umgelöst wird. Schmp. 122–123° ($C_{21}H_{16}O_4$ (332,3). Ber. C, 75,89; H, 4,85. Gef. C, 75,92; H, 5,03).

cis-5-*Phenyl-penten*-2-*dion*-4,5-*al-diäthylacetal*-1 (IX). 20 g *anti*-Furyl-2-phenyl-ketoxim-tosylat (VI)[3] werden in 100 ml 95%-igem Äthanol 3 Tage geschüttelt. Hierauf saugt man das ausgeschiedene Ammoniumtosylat ab (6,3 g), engt das Filtrat in Vakuum ein, schüttelt den Rückstand mit 100 ml Äther und 100 ml Wasser zusammen und filtriert einen ungelösten, nicht näher untersuchten Stoff aus (1,6 g). Die wässrige Schicht enthält noch ca. 3 g Ammoniumtosylat. Die ätherische Lösung wird nach Trocknen mit Natriumsulfat eingedampft und der Rückstand in Vakuum destilliert. Man erhält 9,3 g (61%) Diäthylacetal (IX) in Form einer in wasser unlöslichen gelblichen Flüssigkeit. Siedepunkt 120-123°, 0,2 mm ($C_{15}H_{18}O_4$ (262,3). Ber. C, 68,68; H, 6,92. Gef. C, 68,72; H, 6,71).

Die Oxydation von (IX) *mit Wasserstoffperoxyd*. Eine Lösung von 3,5 g Substanz (IX) in 25 ml Eisessig wird mit 35 cm^3 15%-igem Wasserstoffperoxyd 4 Stunden rückfliessend gekocht und nachher in Vakuum eingedampft. Den Rückstand zieht man in mehreren Anteilen mit 35 ml Benzol aus, dampft die Lösung ein und kristallisiert die zurückgebliebene Substanz aus heissem Wasser um. Sie erwies sich nach Schmp. und Mischschmp. (121°) als Benzoesäure. Ausbeute 1,3 g (80%). Der in Benzol unlösliche Anteil (1,1 g) wurde aus Wasser umkristallisiert und erwies sich nach Schmp. und Mischschmp. (132°) als Maleinsäure. Sie lieferte bei der Sublimation mit Phosphorpentoxyd Maleinsäureanhydrid.

5-*Phenyl-pentan-dion*-4,5-*al-diäthylacetal*-1 (XV). 7,6 g *cis*-5-Phenyl-penten-2-dion-4,5-al-diäthylacetal-1 (IX) werden in 45 ml 95%-igem Äthanol in Gegenwart von 0,8 g Palladium-Kohle (8% Pd) hydriert. Nach Aufnahme von 1 Mol Wasserstoff (ca. 90 Minuten) wird die vom Katalisator filtrierte Lösung eingedampft und der Rückstand in Vakuum destilliert. Siedepunkt 109–112°, 0,2 mm. Man erhält 6,5 g (85%) einer hell grünlich gelben Flüssigkeit ($C_{15}H_{20}O_4$ (264,3). Ber. C, 68,16; H, 7,63. Gef. C, 68,46; H, 7,30).

Oxydation von 5-*Phenyl-pentan-dion*-4, 5-*al-diäthylacetal*-1 *mit Wasserstoffperoxyd*.

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Abb. 1.

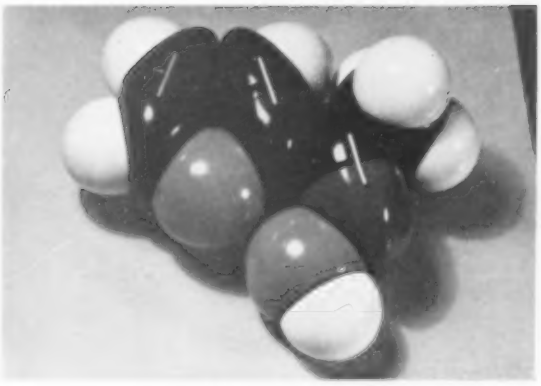

Abb. 2.

Eine Lösung von 1 g Acetal in 10 ml Eisessig wird mit 10 ml 15%-igem Wasserstoffperoxyd 4 Stunden rückfliessend gekocht und dann in Vakuum eingedampft. Den Rückstand rührt man mit 15 ml kaltem Wasser an, saugt die ungelöste Substanz ab und kristallisiert sie aus Wasser um. Sie erwies sich nach Schmp. und Mischschmp. (121)° als Benzoesäure. Ausbeute 0,4 g (87%). Nach Eindampfen der wässrigen Lösung erhält man 0,43 g unreine Bernsteinsäure, welche mit 1,5 ml Acetylchlorid 30 Minuten rückfliessend gekocht wird. Nach Abkühlen mit Eis wird die ausgeschiedene Substanz abfiltriert, mit wenig Äther gewaschen und aus Chloroform umkristallisiert. Die Substanz erwies sich nach Schmp. und Mischschmp. (120°) als Bernsteinsäureanhydrid.

Lävulinsäure-äthylester aus anti-5-*Methyl-furyl-2-methyl-ketoxim-tosylat* (V) 23,5 g Substanz V[3] werden in 118 ml 95%-igem Äthanol geschüttelt. Die Substanz geht unter Wärmeentwicklung und Ausscheidung von Ammoniumtosylat allmählich in Lösung. Die Temperatur wird durch Kühlung unter 30° gehalten. Nach 2 tägigen Stehen wird das ausgeschiedene *p*-toluolsulfonsaure Ammonium abgesaugt (10,1 g), das Filtrat, welches auch Äthylacetat enthält, in Vakuum eingedampft, der Rückstand in 120 ml Äther und 30 ml Wasser aufgenommen und die wässrige Schicht noch fünfmal mit je 25 ml Äther ausgeschüttelt. Hierauf werden die vereinigtenätherische Lösungen nach Trocknen mit Natriumsulfat eingedampft und der Rückstand in Vakuum destilliert. Siedepunkt 79–80° unter 3 mm. Ausbeute 5,8 g (50%) ($C_7H_{12}O_3$ (144,2). Ber. C, 58,31; H, 8,39; C_2H_5O, 31,0. Gef. C, 58,38; H, 8,30; C_2H_5O, 30,0. Molgewicht, 141).

Der Ester gibt in wässrigem Medium ein Semicarbazon, welches nach Umkristallisieren aus Aceton bei 153° schmilzt und seine Mischung mit authentischem Lävulinsäure-äthylestersemicarbazon keine Depression zeigt ($C_8H_{15}O_3N_3$ (201,2). Ber. C, 47,75; H, 7,51; N, 20,88. Gef. C, 47,85; H, 7,46; N, 20,73).

Zur weiteren Identifizierung wurden 5 g Ester in 50 cm³. 2%-iger Schwefelsäure 30 Minuten gekocht und dann 3/4 des Lösungsmittels abdestilliert. Im Destillat konnte der äthanol als *p*-Nitrobenzoat von Schmp. 57° nachgewiesen werden. Aus dem Äther-Extrakt des wässrigen Destillationsrückstandes erhielt man Lävulinsäure (Siedepunkt 134–135°), welche in wässrigem Medium mit Semicarbazidhydrochlorid und Natriumacetat Lävulinsäure-semicarbazon von Schmp. 187–188° lieferte. Eine Mischprobe mit authentischem Lävulinsäure-semicarbazon ergab keine Schmelzpunktdepression.

Lavulinsäure-methylester aus (V). Der Methylester wurde aus 59 g (V) mit 300 cm³ 95%-igem Methanol analog dem Äthylester gewonnen. Aus dem Reaktionsprodukt konnte neben Ammoniumtosylat und Essigsäure 13,8 g (53%) Lävulinsäuremethylester isoliert werden. Siedepunkt 62–64° bei 3 mm ($C_6H_{10}O_3$ (130,1). Ber. C, 55,37; H, 7,74; Gef. C, 55,68; H, 7,72).

Der Ester liefert ein Semicarbazon, welches nach Umkristallisieren aus 50%-igem Methanol bei 148–149° schmilzt. Eine Mischung mit authentischem Lävulinsäuremethylester-semicarbazon schmolz ebenfalls bei 148–149°.

Die Reaktion von syn-*Furyl-2-methyl-ketoxim-tosylat* (syn-I) *mit Äthanol.* Nach 5-tägigen Schütteln von 6 g *syn*-(I)[3] in 30 ml 95%-igem Äthanol bei Zimmertemperatur wurde die Substanz quantitativ unverändert zurückgewonnen. Schmp. 74°.

Nach 5-tägigem Kochen schied sich 1 g Ammoniumstoylat aus. Das dunkelbraune alkoholische Filtrat lieferte nach Eindampfen einen braunen Rückstand.

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Dieser wurde in Äther gelöst, die Lösung mit Wasser gewaschen, eingedampft und der Rückstand aus Wasser umkristallisiert. Die Substanz erwies sich als unverändertes *syn*-(I) von Schmp. 88°.

Wir danken herzlichst Herrn I. Trummer für die Photographien der Kalottmodelle und Frln. Lenke Szabó für die Mikroanalysen.

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UNTERSUCHUNGEN ÜBER FURAN-VERBINDUNGEN—VII

UMWANDLUNG VON 2-ACYL-BENZOFURAN-DERIVATEN IN CHROMONOL-DERIVATE*

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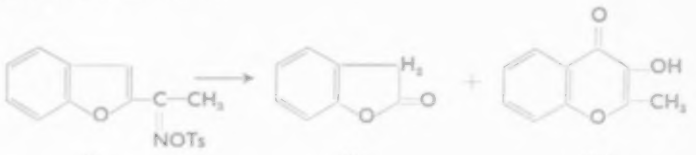
(*Received* 2 *July* 1957)

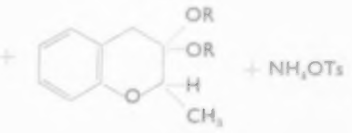
Zusammenfassung—Die Reaktionen der Benzofuryl-2-methyl und Benzofuryl-2-phenyl-ketoxim-*p*-toluolsulfonate (I, V) mit Äthanol und Methanol verlaufen konfigurationsabhängig. Die *anti*-Benzofuryl-Derivate liefern neben anderen Produkten Chromonole (2-Methyl-3-hydroxy-chromon, bzw. Flavonol), *syn*-(V) erleidet eine Beckmann'sche Umlagerung unter Bildung von Benzofuran-2-carbonsäure-anilid, während *syn*-(I) unverändert bleibt.

Abstract—The reactions of benzofuryl-2-methyl-, and of benzofuryl-2-phenyl-ketoxime *p*-toluenesulfonates (I,V), with ethanol and methanol proceed according to their configurations. The *anti*-benzofuryl derivatives afford among other products chromonoles (2-methyl-3-hydroxy-chromone and flavonol, respectively), *syn*-(V) undergoes Beckmann rearrangement yielding benzofuran-2-carbonic acid-anilide, whereas *syn*-(I) remains unchanged.

ES WURDE vor einigen Jahren gezeigt,[1] dass bei der Einwirkung von Äthanol, oder Methanol auf das Tosylat des Benzofuryl-2-methyl-ketoxims (I) neben Ammonium-p-toluolsulfonat drei verschiedene Produkte : *o*-Hydroxy-phenyl-essigsäurelacton (2-Cumaranon, II), 2-Methyl-3-hydroxy-chromon (III) und eine Flüssigkeit, welcher mit vorbehalt die Acetal Formel (IV) (Dimethyl-, bzw. Diäthyl-acetal der Keto-Form von III) zugeteilt wurde, entstehen:



(I) (II) (III)



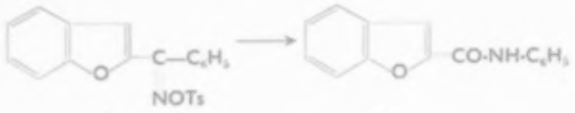
(IV)

Aus präparativem Gesichtspunkt schien uns die Bildung der Chromon-Derivate (III) and IV interessant, weil anzunehmen war, dass eine analoge Umsetzung entsprechend substituierter Benzofuryl-ketoxim-tosylate zu Flavonol, bzw. zu schwer zugänglichen Flavonol-Derivaten führen könnte. Als wir aber die Reaktion mit dem

* Im Auszug vorgetragen auf der Tagung der Chemischen Gesellschaft in der DDR am 22, Oktober 1955, Zu Leipzig.

[1] L. Vargha, J. Ramonczai und J. Báthory *J. Amer. Chem. Soc.* **71**, 2652 (1949).

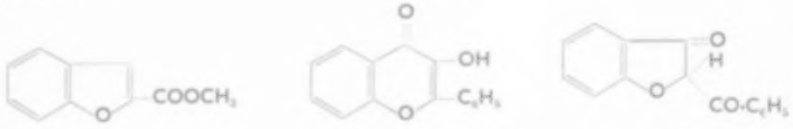
Tosylat des bekannten Benzofuryl-2-phenyl-ketoxims (V) ausführten, erhielten wir an Stelle des erwarteten Flavonols, als einziges Produkt Benzfuranilid[2] (VI):



(V) (VI)

Die Bildung von (II) and (VI) durch Beckmann'sche Umlagerungen deutete auf die *anti*-Benzofuryl-Konfiguration von (I) und auf die *syn*-Benzofuryl-Konfiguration von (V).

Neuerdings haben Geissman und Armen[3] unsere Versuche überprüft und offenbar in Unkenntnis unserer IV Mitteilung[2] teilweise über abweichende Ergebnisse berichtet. Sie haben nämlich aus dem Reaktionsprodukt von (V) mit Methanol ausser (VI) noch Benzofuran-carbonsäure-methylester (VII), Flavonol (VIII) und 2-Benzoyl-cumaranon-3 (IX) isoliert.



(VII) (VIII) (IX)

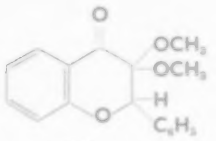
Da in der VI Mitteilung[4] gezeigt werden konnte, dass die Umwandlung der einfachen 2-Furyl-ketoxim-tosylate mit Alkoholen konfigurationsabhängig ist, war eine analoge Stereospezifität auch in der Benzofuran-Reihe wahrscheinlich. Es war also anzunehmen, dass *syn*-(V) eine Beckmann'sche Umlagerung unter Bildung von (VI) erleidet, während *anti*-(V) in Analogie zu (I) auch Flavonol liefert. Die gleichzeitige Bildung von (VI), VII), (VIII) und (IX) in den Versuchen von Geissman und Armen könnte danach darauf zurückgeführt werden, dass sie ein Gemisch der beiden isomeren (V) in den Händen gehabt haben. Diese Vermutung hat sich nach unseren neueren Arbeiten[5] als richtig erwiesen, denn das *syn*-Benzofuran-2-phenyl-ketoxim schmilzt bei 145°, das *anti*-Derivat bei 156°, während Geissman und Armen 128–129,5° angeben und das zur Reaktion verwendete Tosylat (V) keinerlei Reinigung unterworfen hatten.

Nach diesen Überlegungen schien es uns wünschenswert, die Versuche mit den sterisch einheitlichen Tosylaten zu wiederholen. Die Versuche haben unsere Annahme über die Konfigurationsabhängigkeit des Reaktionsverlaufs vollauf bestätigt, *syn*-(I) blieb auch nach 16 stündigem Kochen in 95%-igem Äthanol unverändert, während *syn*-(V) schon nach 3 stündigem Kochen in 92%-igem Methanol in Folge von Beckmann'scher Umlagerung (VI) und teilweiser Alkoholyse des primär gebildeten (VI) Benzofuran-carbonsäure-methyl-ester (VII) lieferte, aber gar kein Flavonol.

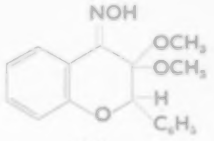
Auch die Reaktion von *anti*-(V) verlief nach unseren Erwartungen. Es lieferte nämlich weder Benzofuran-2-carbonsäure-anilid (VI), noch den Ester (VII), sondern nur Flavonol in 15% Ausbeute und eine Substanz von Schmp. 113-114° in 50-60%

[2] L. Vargha und F. Gönczy *J. Amer. Chem. Soc.* **72**, 2738 (1950).
[3] T. A. Geissman und A. Armen *J. Amer. Chem. Soc.* **77**, 1623 (1955).
[4] L. Vargha und G. Ocskay *Tetrahedron* **2**, 151 (1958).
[5] G. Ocskay und L. Vargha. *Tetrahedron* **2**, 140 (1958).

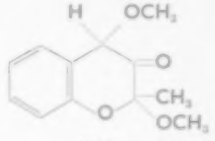
Ausbeute, welche Geissman und Armen nicht gefunden haben. Auf die Isolierung des 2-Benzoyl-cumaranon-3 (IX) haben wir verzichtet, zumal diese Substanz auch in den Versuchen der amerikanischen Forscher nur in vernachlässigbarer Menge entstand. Die Substanz von Schmp. 113–114° stellt nach Analyse und Eigenschaften ein Analogon des Acetals (IV) dar, denn sie liefert mit Hydroxylamin—wie (IV)—ein Oxim, aus dem durch saure Hydrolyse leicht und mit guter Ausbeute das Phenyl-Analogon von (III), das Flavonol entsteht. Daher teilen wir der Substanz vorläufig Formel (X) (2-Phenyl-chromanon-3-dimethylacetal) und seinem Oxim Formel (XI) zu, mit der Bemerkung, dass die ungewöhnliche Beständigkeit von (X) und (IV), gegenüber Säuren dem Vorhandensein einer Acetal-Bindung zu widersprechen scheint.



(X)



(XI)



(XII)

Geissman und Armen[3] schreiben dem "Acetal" (IV) ohne hinreichende experimentelle Begründung Formel (XII) zu, trotzdem sie die schwere Hydrolysierbarkeit der Acetal-Bindung in (IV) theoretisch für möglich erklären. Die Frage bedarf nach unserer Meinung weiterer experimenteller Bearbeitung.

Um die Bildung der Chromonol-Derivate (III, IV, VIII und X) aus den Benzofuran-Derivaten (I, V) zu deuten, schlagen Geissman und Armen[3] einen zehnstufigen Reaktionsweg vor, in dem das "Acetal" von der nicht genügend bewiesenen Formel (XII) als Zwischenprodukt angenommen wird. Wir halten indessen dieses Reaktionsschema unter anderen wegen der Stabilität des "Acetals" (IV, bzw. XII und X) wenig wahrscheinlich. Es scheint uns kaum möglich, dass das "Acetal", welches beim Kochen mit starken Säuren und Alkalien unverändert bleibt, unter den milden Reaktionsbedingungen als Zwischenprodukt fungieren könnte.

Bei Erwägung des Reaktionsmechanismus soll man nach unserer Meinung die folgenden Beobachtungen berücksichtigen.

(1) Die Bildung der ungesättigten Trioxo-Verbindungen aus den einfachen Furyl-2-ketoxim-tosylaten[4] und der Chromonol-Abkömmlinge aus den analogen Benzofuryl-Derivaten geht unter identischen Versuchsbedingungen vor sich.

(2) Die Reaktionen sind in beiden Reihen konfigurations abhängig.[4]

(3) In der Reaktion von *anti*-(I) bilden sich das Chromonol-Derivat (III) und das Cumaranon (II) durch Beckmann'sche Umlagerung gleichzeitig.[1] Diese Tatsachen legen den Gedanken nahe, dass all diese Umwandlungen eine gemeinsame Anfangsphase durchlaufen.

Auf eine ausführliche Darstellung der Chromonol-Bildung möchten wir jedoch wegen Mangel an beweisendem Tatsachenmaterial vorläufig verzichten.

BESCHREIBUNG DER VERSUCHE

Die Reaktion des anti-*Benzofuryl-2 phenyl-ketoxim-tosylats* (anti-V) *mit Methanol. Bildung von Flavonol* (VIII) *und 2-Phenyl-chromanon-3-dimethylacetal* (X)[2]. Eine Lösung von 15,4 g *anti*-(V) in 123 ml Methanol und 12 ml Wasser werden 2,5

Stunden rückfliessend gekocht. Am nächsten Tage dampfte man die orange farbene Lösung in Vakuum ein, nahm den Rückstand in 100 ml Äther und 50 ml Wasser auf und schüttelte die wässrige Schicht noch mehrmals mit Äther aus. Die wässrige Schicht enthält nach der Analyse 5,8 g (78%) Ammonium-*p*-toluol-sulfonat. Die vereinigten Äther-Auszüge schüttelt man 7-mal mit je 40 ml 5%-iger Natriumhydrogencarbonat-Lösung aus. Aus der Bicarbonat-Lösung fällt nach Ansäuern ein wenig flockiger Niederschlag, vermutlich Benzoyl-cumaronon (IX)[3] aus.

Der Äther-Anteil wird dann 10-mal mit je 40 ml n-Natronlauge ausgeschüttelt und der alkalische Auszug mit 5 n-Schwefelsäure angesäuert. Das ausgefallene Flavonol (1,45 g; 15,5%) schmilzt nach Umkristallisieren aus Äthanol bei 168° und zeigt keine Schmelzpunktserniedrigung in Gemisch mit einem authentischem Präparat.

Der nach Eindampfen der Äther-Lösung erhältliche Rückstand destilliert unter 0,2 mm bei 147–149°. Das grünlich gelbe Destillat (5,2 g) wird zuerst aus wässrigem Äthanol, dann aus Benzin umkristallisiert. Das in farblosen Kristallen erhaltene (X) schmilzt bei 113–114° und ist gegenüber Säuren und Alkalien sehr beständig. Eine Lösung von 0,5 Substanz in 10 ml Äthanol bleibt nach 48 stündigem Kochen mit 10 ml 20%–iger Schwefelsäure, oder 10 ml 5n–Natronlauge unverändert ($C_{17}H_{16}O_4$ (284,3). Ber. C, 71,82; H, 5,67. Gef. C, 71,85; H, 5,94).

Oxim aus X (XI,).[2] Ein Gemisch von 0,56 g Acetal (X), 0,2 g Hydroxylammoniumchlorid, 0,2 g wasserfreiem Natriumacetat und 6 ml Äthanol wird 4 Stunden auf dem Wasserbade erhitzt. Nach Abdestillieren des Alkohols in Vakuum gibt man zum Rückstand wenig Wasser. Das bei Kühlung und Reiben auskristallisierte Oxim (0,5 g; 83%), wird aus wässrigem Aceton umgelöst. Schmp. 191° ($C_{17}H_{17}O_4N$ (299,3). Ber. C, 68,21; H, 5,72; N, 4,68. Gef. C, 68,51; H, 5,75; N, 4,78).

Flavonol aus dem Oxim XI. 0,4 g Oxim (XI) werden in einem Gemisch von 5 ml Äthanol und 5 ml 2n–Schwefelsäure 2 Stunden auf dem Wasserbade erhitzt. Beim Stehen über Nacht scheiden sich gelbe Nadeln aus, welche aus äthanol umkristallisiert werden. Die Substanz erwies sich nach Schmp. (168°) und Mischschmp. als Flavonol. Ausbeute 80%.

Die Reaktion des syn-*Benzofuryl-2-phenyl-ketoxim-tosylats* (syn-V) *mit Methanol. Bildung von Benzofuran-2-carbonsäure-anilid* (VI) *und Benzofuran-2-carbonsäure-methylester* (VII). 12 g *syn*-(V) werden in einem Gemisch von 96 ml Methanol und 8 ml Wasser 3 Stunden auf dem Wasserbade erhitzt. Man dampft das Reaktionsgemisch in Vakuum ein und löst den Rückstand in 100 ml Äther und 22 ml Wasser auf. Die saure wässrige Lösung enthält 3,7 g (70%) *p*-Toluolsulfosäure, welche nach Neutralisieren mit Ammoniak in Form ihres Ammoniumsalzes isoliert wurde.

Aus dem alkalischen Auszug der Äther-Lösung konnte kein Flavonol, oder Benzoyl-cumaranon gewonnen werden.

Den Rückstand der Äther-Lösung kristallisiert man aus 75%–igem Äthanol um. Man erhält 1,6 g (22%) farblose Substanz, welche sich nach Schmp. (156–157°) und Mischschmp. als Benzofuran-2-carbonsäure-anilid erwiesen hat ($C_{15}H_{11}O_2N$) (237,2). Ber. C, 75,95; H, 4,67; N, 5,90. Gef. C, 76,14; H, 4,52; N, 6,15).

Den durch Eindampfen der alkoholischen Mutterlauge erhaltenen Rückstand destilliert man im Vakuum ab. Siedepunkt 185–190°. Man gewinnt 2,7 g (50%) Benzofuran-2-carbonsäure-methyl-ester von Schmp. 50–51°. Zur Identifizierung wurde der Ester mit 2 n-Natronlauge verseift und die erhaltene Substanz aus Benzol

umkristallisiert. Schmp. 191–192°, eine Mischprobe mit authentischer Cumarylsäure ergab keine Schmelzpunktserniedrigung.

Die Behandlung von syn-*Benzofuryl-2-methylketoxim-tosylat* (syn-I) *mit Methanol.* 0,6 g *syn*-(I) wurden in 6 ml 95%-igem Äthanol 16 Stunden gekocht. 93% der Substanz konnten unverändert zurückgewonnen werden. Nach 10 tägigem Kochen betrug die Menge des unverändert gebliebenen *syn*(-I) nur 0,1 g neben 0,2 g (58% d.Th.) Ammonium-*p*-toluolsulfonat.

Für die Mikroanalysen dankenwir Frln. Lenke Szabó verbindlichst.

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PRELIMINARY COMMUNICATIONS

Steroids—XC*

11α-Methyl-11β-hydroxy steroids

(*Received* 24 *September* 1957)

We wish to record the synthesis of several 11α-methyl-11β-hydroxy steroid hormone analogs derived by the addition of metallo-organic reagents to the C-11 position of 11-keto steroids.[1]†‡ Reaction of androstan-3β-ol-11,17-dione (I)§ (m.p. 169–171°, $[\alpha]_D$ + 125°.‖ *Anal.* Found for $C_{19}H_{28}O_3$: C, 74·56; H, 8·98) with methylmagnesium bromide in benzene-ether solution at 25° gave, in addition to the expected 17α-methylandrostane-3β,17β-diol-11-one (m.p. 218–221°, $[\alpha]_D \pm 0°$), a 30 per cent yield of a more polar by-product (II) (m.p. 164–166°, $[\alpha]_D$ − 5°. *Anal.* Found for $C_{21}H_{36}O_3$: C, 75·32; H, 10·91) to which we assign the 11α,¶17α-dimethylandrostane-3β,11β,17β-triol structure, since it exhibited no carbonyl absorption in the infrared and differed from 17α-methylandrostane-3β,-11β,17β-triol.** Substitution of methyllithium in ether for methylmagnesium bromide gave an 80 per cent yield of the same 11,17-dimethyl compound.

Pyridinium-chromate oxidation of (II) smoothly led to the 3-keto compound, 11α,17α-dimethyl-androstane-11β,17β-diol-3-one (III) (m.p. 202–205°, $[\alpha]_D$ + 6°. *Anal.* Calcd. for $C_{21}H_{34}O_3$: C, 75·40; H, 10·24. Found C, 75·03; H, 10·08).

Confirmation and extension of 11-methyl addition was provided by the reaction with methyl-lithium of mono-functional 11-keto compounds, such as pregnan-11-one[2] and allopregnan-11-one,[2] which yielded ketone-free products, resistant to chromic acid oxidation, e.g. 11α-methyl-allopregnan-11β-ol (m.p. 112–113°, $[\alpha]_D$ + 23°. *Anal.* Found for $C_{22}H_{38}O$: C, 83·17; H, 11·77; O, 4·89).

Although a number of more complex molecules failed to react at C-11 with methyllithium, 11α-methyl-11β-hydroxytestosterone (IV) was readily derived by the following reaction sequence. Adrenosterone 3,17-bis*cyclo*ethylene ketal[3] was converted to 11α-methyl-3,17-di*cyclo*ethylenedioxy-Δ⁵-androsten-11β-ol (V) (m.p. 192–194°, $[\alpha]_D$ − 94° (pyr.). *Anal.* Found for $C_{23}H_{36}O_3$: C, 70·90; H, 9·01) by reaction with methyllithium in ether-tetrahydrofuran solution. Hydrolysis of the ketal moieties of (V) in 70 per cent acetic acid gave 11α-methyl-Δ⁴-androsten-11β-ol-3,17-dione (VI) (m.p. 151–152°, $[\alpha]_D$ + 162°, $\lambda_{max.}^{EtOH}$ 243 mμ, log ε 4·19. *Anal.* Found for $C_{20}H_{28}O_3$: C, 75·61;

* Paper LXXXIX, A. Bowers, H. J. Ringold and R. I. Dorfman *J. Amer. Chem. Soc.* **79**, 4556 (1957).

† Ruzicka *et al.* reported the addition of methylmagnesium iodide to the triterpene, 11-keto-β-amyrin, but it should be noted that they were dealing with an α,β-unsaturated carbonyl function.

‡ The addition of methylmagnesium bromide to a steroidal C-11 carbonyl function was reported in the case of the ring A unsubstituted androstane-11,17-dione in a talk given at the Dallas Meeting of the American Chemical Society, April 1956, by Dr. John C. Babcock of The Upjohn Company.

§ Prepared by sodium bismuthate cleavage of allopregnane-3β,17α,21-triol-11,20-dione.

‖ All melting points are uncorrected and rotations were determined at 20° in chloroform. We are grateful to Mrs. E. Necoechea, Miss G. Monroy and Miss J. Lisci for their valuable technical assistance and to Mr. E. Avila for determination of rotations and spectra.

¶ Carbanion addition would be expected to follow the stereochemical course of hydride attack and thus yield the 11α-methyl compound.

** This compound, prepared by the addition of methylmagnesium bromide to androstane-3β,11β-diol-17-one, melts at 247–251°, $[\alpha]_D$ + 12°. *Anal.* Found for $C_{20}H_{34}O_3$: C, 74·14; H, 10·52. While reduction of hindered ketones with methyl Grignard reagents has not been described nor would such reduction appear to be mechanistically feasible, in contrast to the corresponding ethyl reagent, we did not wish to discount this possibility *a priori*.

[1] L. Ruzicka, G. Müller and H. Schellenberg *Helv. Chim. Acta* **22**, 767 (1939).
[2] F. Sondheimer, E. Batres and G. Rosenkranz *J. Org. Chem.* **22**, 1090 (1957).
[3] S. Bernstein, R. Littell and J. H. Williams *J. Amer. Chem. Soc.* **75**, 1481 (1953).

H, 8·89) which was converted to the testosterone analog (IV) (m.p. 255–256°, $[\alpha]_D$ + 111°, $\lambda_{max.}^{EtOH}$ 244 mμ, log ε 4·18. *Anal.* Found for $C_{20}H_{30}O_2$: C, 75·24; H, 9·62) by selective reduction[4] with sodium borohydride in methanol at 0°. Alternately, reaction of the 3,17-dione (VI) with pyrrolidine in methanol gave the 3-enamine,[5] (11α-methyl-3-(N-pyrrolidyl)-$\Delta^{2,5}$-androstadien-11β-ol-17-one (VII) (m.p. 249–250°, $[\alpha]_D$ − 140° (pyr.), $\lambda_{max.}^{Ether}$ 281 mμ, log ε 4·35. *Anal.* Found for $C_{24}H_{35}NO_2$: C, 77·87; H, 9·43; N, 3·85) which, after lithium aluminum hydride reduction followed by hydrolysis, gave authentic (IV).

We shall report at a later date on further interconversions in this interesting series, as well as on the dehydration products of 11α-methyl-11β-hydroxy steroids.

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[4] J. K. Norymberski and G. F. Woods *J. Chem. Soc.* 3426 (1955).
[5] J. Johnson, M. Herr, J. Babcock, A. Fonken, J. Stafford and F. Heyl *J. Amer. Chem. Soc.* **78**, 430 (1956).

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Steroids—XCI *

Microbiological oxidations of 19-norprogesterone

(*Received* 24 *September* 1957)

The clinical importance of 19-nor steroids such as 19-nor-17α-methyltestosterone,[1] 19-nor-17α-ethinyltestosterone (Norlutin)[1] and of the latter's $\Delta^{5(10)}$-isomer[2] is now well recognized† and these substances are all prepared on an industrial scale by modified Birch reductions[3] of aromatic precursors. The synthesis of the more complicated 19-nor analogs of 11-oxygenated adrenal hormones,[4] on the other hand, has been carried out only by adrenal incubation[4] of 19-norpregnenes or by starting with 11-oxygenated aromatic precursors[5] amenable to Birch reduction.[3] The much more attractive and direct route of attempting 11-oxygenation in the 19-nor series by microbiological means has so far only been accomplished with 19-nortestosterone[6] and is thus of no direct utility for the facile synthesis of 19-nor cortical hormones.[4] We should now like to report that 19-norprogesterone (I)[7] reacts readily with a variety of micro-organisms and that the way is now open to the synthesis of a large number of 11-oxygenated-19-nor as well as 11-oxygenated aromatic analogs of steroidal hormones of the pregnane series.

Incubation of (I) for 24 hr at 28° with *Rhizopus nigricans* (ATCC no. 6227b) in a medium containing peptone and corn molasses, furnished in ca. 70 per cent yield 11α-hydroxy-19-norprogesterone (II) (m.p. 171–173°, $[\alpha]_D$ + 62° ($CHCl_3$),‡ $\lambda_{max.}^{EtOH}$ 242 mμ, log ε 4·22; *Anal.* Found for

* Paper XC. H. J. Ringold, E. Batres and J. A. Zderic *Tetrahedron.* **2**, 164 (1958).

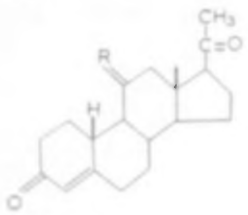
† New York Academy of Sciences Conference on *New Steroid Compounds with Progestational Activity*, New York City, October 7–8, 1957.

‡ The 11α-hydroxy assignment is also consistent with molecular rotation data: ΔM_D 11α-hydroxy-19-norprogesterone→19-norprogesterone + 245 as compared to ΔM_D 11α-hydroxy-19-nortestosterone→19-nortestosterone + 284.[6]

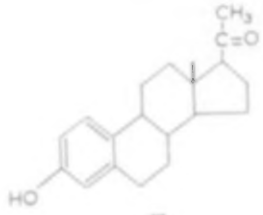
[1] C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer *J. Amer. Chem. Soc.* **76**, 4092 (1954); Abstracts, Milwaukee A.C.S. Meeting p. 18J, April, 1952; U.S. patents 2,744,122 and 2,774,777.
[2] F. B. Colton U.S. patent 2,725,389.
[3] A. J. Birch *Quart. Rev. Chem. Soc. Lond.* **4**, 69 (1950); *J. Chem. Soc.* 367 (1950).
[4] A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas and C. Djerassi *J. Amer. Chem. Soc.* **76**, 6210 (1954).
[5] B. J. Magerlein and J. A. Hogg *J. Amer. Chem. Soc.* **79**, 1508 (1957).
[6] R. L. Pederson, J. A. Campbell, J. C. Babcock, S. H. Eppstein, H. C. Murray, A. Weintraub, R. C. Meeks, P. D. Meister, L. M. Reineke and D. H. Peterson *J. Amer. Chem. Soc.* **78**, 1512 (1956).
[7] C. Djerassi, L. Miramontes and G. Rosenkranz *J. Amer. Chem. Soc.* **75**, 4440 (1953).

$C_{20}H_{28}O_3$: C, 75·62; H, 8·87; O, 15·21) while similar treatment of (I) with *Curvularia lunata* (Syntex strain 192) provided 11β-hydroxy-19-norprogesterone (III) (m.p. 215–217°, $[\alpha]_D$ + 158° ($CHCl_3$), $\lambda_{max.}^{EtOH}$ 242 mμ, log ε 4·20; *Anal.* Found for $C_{20}H_{28}O_3$: C, 75·83; H, 8·81). Other strains of *Rhizopus nigricans* (ATCC no. 10404) as well as other organisms such as *Rhizopus arrhizus* (ATCC no. 11145), *Helicostylum piriforme* (ATCC no. 8992) and *Absidia coerulea* (ATCC no. 1359b) effected monohydroxylation of 19-norprogesterone.

The structure assignments follow from the following observations. Both (II) and (III) upon chromium trioxide oxidation furnished the same ketone, 11-keto-19-norprogesterone (IV) (m.p. 175–176°, $[\alpha]_D$ + 284° ($CHCl_3$), $\lambda_{max.}^{EtOH}$ 240 mμ, log ε 4·20, $\lambda_{max.}^{CHCl_3}$ 5·87, 6·0 and 6·16 μ; *Anal.* Found for $C_{20}H_{26}O_3$: C, 76·32; H, 8·31; O, 15·32), thus demonstrating that both hydroxylation products are epimers and that oxygenation did not occur at a tertiary carbon atom. The infrared spectrum of the common oxidation product (IV) requires that the newly introduced hydroxyl group forms part of a six-membered ring and the position of the ultraviolet absorption maxima of (II), (III) and (IV), which remain unchanged in alkali, as well as the stability of (II) and (III) towards alkali eliminate all positions except for C-11 and C-12. Since microbiological oxidation of a steroid at C-12 has so far not been observed,[8] the presence of an oxygen atom at C-11 in (II), (III) and (IV) appears to be established.



I R = H_2
II R = α-OH, β-H
III R = β-OH, α-H
IV R = O



V

The introduction of a double bond at positions 1 and 2 in Δ^4-3-keto steroids by microbiological means[9] is now well known. When applied to a 19-nor-Δ^4-3-keto steroid, such a reaction should lead directly to the corresponding phenol. In fact, such a transformation—in the case of 19-nortestosterone leading to estradiol and estrone—has been recorded very recently[9] and this enzymatic reaction may well be of biochemical significance in the formation of estrogens.

We have observed that such a microbiological aromatization proceeds with equal facility with 19-norprogesterone (I)[7] and that incubation of (I) for 72 hr with *Corynebacterium simplex* (ATCC no. 6946) produces in over 60 per cent yield by direct crystallization 3-hydroxy-17β-acetyl-1,3,5(10)-estratriene (V) (m.p. 238–240°, $[\alpha]_D$ + 164° ($CHCl_3$), λ_{max}^{EtOH} 280–282 mμ, log ε 3·30) identified by direct comparison with an authentic specimen.[10]

The preparation of hitherto inaccessible aromatic 11-oxygenated pregnenes by a combination of microbiological hydroxylation and dehydrogenation of 19-norpregnenes will be reported at a future date.

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[8] A. Wettstein *Experientia* **11,** 465 (1955); G. M. Shull *Trans. N.Y. Acad. Sci.* II **19,** 147 (1956); S. H. Eppstein, P. D. Meister, H. C. Murray and D. H. Peterson *Vitamins and Hormones* Vol. 14, p. 359 New York, Academic Press (1956).
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Tetrahedron, 1958, Vol. 2, pp. 168a–172. Pergamon Press Ltd., London

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ALKALOID STUDIES—XXI*

PARTIAL STRUCTURE OF CASIMIROEDINE†

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(*Received* 5 *November* 1957)

Abstract—Degradation experiments are reported which demonstrate that the alkaloid casimiroedine contains the N-cinnamoyl-N-methyl-histamine moiety.

CASIMIROEDINE, the principal alkaloid of the seeds of *Casimiroa edulis* La Llave et Lej., has already been isolated in 1911,[1] but its correct empirical formula ($C_{21}H_{27}N_3O_6$) has been established only very recently.[2,3] Preliminary characterization experiments[3] involving acid or basic hydrolysis demonstrated that casimiroedine is the cinnamic acid amide of a base ($C_{12}H_{21}N_3O_5$)—named casimidine—and it has now been possible to gain further insight into the structure of this interesting alkaloid.

As has already been reported earlier,[3] casimiroedine and some of its derivatives consume 2 moles of periodic acid and this reaction has now been carried out on a preparative scale with dihydrocasimiroedine.§ Initial difficulties in preparing an analytically pure sample of the resulting amorphous amphoteric product ($C_{20}H_{25}N_3O_5$)—apparently due to incorporation of small amounts of iodine[4]—led to purification attempts involving treatment with zinc in acetic acid. Such a procedure afforded material which gave satisfactory analyses but occasionally such zinc treatment provided in poor yield a second substance corresponding to $C_{15}H_{19}N_3O$. The paucity of oxygen atoms in the latter product was greatly encouraging since many of the experimental difficulties—particularly with casimidine—are due to the large number of heteroatoms. Whereas barium hydroxide hydrolysis of dihydrocasimiroedine results[3] simply in cleavage of the amide linkage with formation of dihydrocinnamic acid and the oxygen-rich casimidine ($C_{12}H_{21}N_3O_5$), similar treatment of the periodic acid cleavage products $C_{20}H_{25}N_3O_5$ and $C_{15}H_{19}N_3O$ provided dihydrocinnamic acid and two *oxygen-free* bases. Separation of the bases was achieved by

* Paper XX, C. Djerassi, T. Nakano and J. M. Bobbitt *Tetrahedron* **2**, 58 (1958).

† We are indebted to the National Heart Institute of the National Institutes of Health, U.S. Public Health Service for financial assistance (grant No. H-2574).

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§ Dihydrocasimiroedine shows more favorable solubility characteristics and hence was selected as the starting material instead of the parent alkaloid. As demonstrated earlier[3] hydrogenation involves only saturation of the double bond of cinnamic acid without affecting the rest of the molecule.

[1] F. B. Power and T. Callan *J. Chem. Soc.* 1993 (1911).
[2] A. Aebi *Helv. Chim. Acta* **39**, 1495 (1956).
[3] C. Djerassi, J. Herran, H. N. Khastgir, B. Riniker and J. Romo *J. Org. Chem.* **21**, 1510 (1956).
[4] K. Hofmann *Imidazole and its Derivatives*. Interscience, New York (1953).

fractional crystallization of their picrates, whereupon there was obtained the dipicrate of $C_6H_{11}N_3$ (subsequently shown to be V) and the tripicrate of $C_{11}H_{17}N_5$ (subsequently shown to be VI). When the cleavage of the periodic acid oxidation product was carried out with hydrochloric acid, extensive decomposition occurred and only the dipicrate of the base $C_6H_{11}N_3$ was encountered.

Since casimiroedine (I) possesses only three nitrogen atoms, it is clear that the base $C_{11}H_{17}N_5$ must represent a condensation product and its constitution and probable mode of formation is discussed below. On the other hand, the base $C_6H_{11}N_3$ still contains all of the nitrogen atoms of the parent alkaloid and its structure elucidation would constitute a major advance in our knowledge of the chemistry of casimiroedine. As indicated above, the base was isolated, together with dihydrocinnamic acid, in the hydroysis of the $C_{15}H_{19}N_3O$ fragment—obtained by successive treatment of dihydrocasimiroedine (II) with periodic acid and zinc dust—from which it follows that the latter represents the dihydrocinnamic acid amide of $C_6H_{11}N_3$, which was also confirmed by infrared spectral examination. The amide $C_{15}H_{19}N_3O$ (subsequently shown to be IV) had only one basic nitrogen atom (pK_a' 6·5) and was optically inactive. These properties, coupled with the observations that the base $C_6H_{11}N_3$ contained one N-methyl group, no C-methyl function and exhibited only terminal, ultraviolet absorption strongly suggested a histamine derivative. The melting point of the dipicrate closely resembled that reported[5] for N-methylhistamine (V) and identity was established conclusively by direct comparison with an authentic specimen prepared by treating 4-(β-chloroethyl)-imidazole hydrochloride[6] with methylamine in a sealed tube.

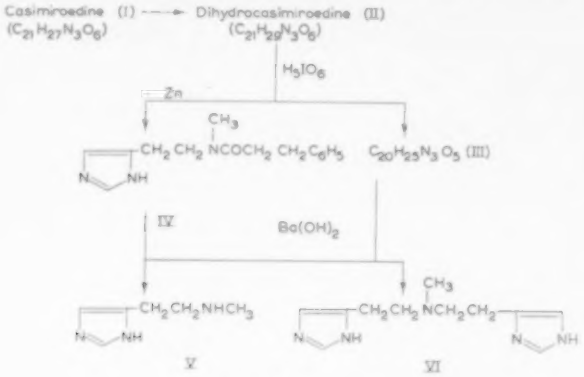
The expected by-product (VI) in the above synthesis—resulting from condensation of 2 moles of 4-(β-chloroethyl)-imidazole with one of methylamine—was also isolated and proved to be identical with the base $C_{11}H_{17}N_5$ derived from dihydrocasimiroedine. The formation of di-β-(4-ethylimidazolyl)-methylamine (VI) in the barium hydroxide hydrolysis of III and IV is apparently due to intermolecular condensation with loss of methylamine.

Electrometric titrations of various casimiroedine derivatives show interesting variations which indicate the marked influence of substituents upon the basicity of the imidazole system.[4] Thus, casimiroedine (I) itself exhibits pK_a' 5·0, N-dihydrocinnamoyl-N-methylhistamine (IV) 6·5 and casimidine 3·8 and 9·85. For comparison with casimidine, histamine was also measured under the same conditions (pK_a' 5·5 and 9·6) and it is obvious that the nitrogen atom of casimiroedine (I) involved in the amide linkage is the strongly basic one in the side chain corresponding to pK_a' 9·85 in casimidine. Consequently, casimiroedine is N-cinnamoyl-N-methylhistamine with the nature and point of attachment of the remaining $C_6H_{10}O_5$ fragment still to be determined. The absence[3] of infrared carbonyl bands in casimidine and the formation of a tetra-acetate[2] and tetrabenzoate[3] of casimiroedine suggest that the $C_6H_{10}O_5$ moiety is probably a sugar. Further work concerning this structural point is now in progress.

Alkaloids containing an imidazole nucleus are very rare[7] and are chiefly limited to the genus *Pilocarpus* of the Rutaceae family. It is interesting to note that

[5] B. Garforth and F. L. Pyman *J. Chem. Soc.* 489 (1935).
[6] C. F. Huebner *J. Amer. Chem. Soc.* **73**, 4667 (1951).
[7] A. R. Battersby and H. T. Openshaw in R. H. F. Manske and H. L. Holmes *The Alkaloids* Vol. III, Chap. 20. Academic Press, New York (1953).

the genus *Casimiroa* belongs to the same plant family and more strikingly, that N, N-dimethylhistamine has recently been encountered[8] in *Casimiroa edulis*.



EXPERIMENTAL*

Periodic acid oxidation of dihydrocasimiroedine (II). A solution of 4·4 g of dihydrocasimiroedine (II)[3] in 80 cm³ of water containing 8·8 g of periodic acid was left at room temperature for 4 hr and the pH of the solution was then adjusted to 6·5† with aqueous sodium hydroxide. Continuous extraction with chloroform for 20 hr yielded 3·75 g of amber-colored oil which could not be crystallized. Chromatography in chloroform solution on Merck acid-washed alumina and washing with the same solvent furnished a trace of material while the bulk was eluted with chloroform–methanol (10 : 1) and represented a colorless foam resistent to crystallization. Homogeneity was demonstrated by the virtual identity of the infrared spectra of various fractions eluted with chloroform–methanol (10 : 1) and in particular by countercurrent distribution. A distribution coefficient of unity was obtained in a solvent system consisting of chloroform–hexane (28 : 12) in the lower phase and methanol–water (3 : 1) in the upper one. Each layer consisted of 25 cm³ and a 28-tube all-glass countercurrent distribution apparatus was employed. The peak fractions (16–19) exhibited the same infrared spectrum as the original chromatogram fractions but for further purification, they were rechromatographed and the amorphous product was dried for 20 hr at 60° under high vacuum.

Anal. Calcd. for $C_{20}H_{25}N_3O_5$: C, 62·00; H, 6·50; N, 10·85; O, 20·65. Found: C, 59·43; H, 6·73; N, 10·83; O, 19·18.

A 1·3 g sample of the above material in 120 cm³ of acetic acid was stirred for 2 hr at 30–40° with 8 g of zinc dust and the resulting product was chromatographed twice before drying for 48 hr at 60° and 0·01 mm; colorless amorphous material liquefying near 125°, no infrared absorption bands between 3·6 and 6·0 μ, $[\alpha]_D$ −3° (*c*, 0·72 in $CHCl_3$), −5° (*c*, 0·68 in 1% HCl), −15° (*c*, 0·7 in 1% NaOH).

* Melting points were determined on the Kofler block. The microanalyses were performed by Mr. Joseph F. Alicino (Metuchen, New Jersey) and Dr. A. Bernhardt (Mülheim, Germany). We are greatly indebted to Dr. Harold Boaz of Eli Lilly Co. (Indianapolis, Indiana) for the electrometric titrations which were carried out in 33% aqueous dimethyl formamide and to Dr. F. Kincl (Syntex, S.A., Mexico City) and Dr. F. A. Hochstein (Chas. Pfizer Co., Brooklyn, New York) for supplies of casimiroedine.

† The product was amphoteric and could not be extracted with chloroform from either a strongly acidic or strongly basic medium.

[8] F. A. Hochstein and J. Ling *New York Section Meeting-in-Miniature*. American Chemical Society (February 15, 1957).

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Anal. Found: C, 61·29; H, 6·71; N, 10·70; O, 20·88.

Subsequently, it was found that analytically pure material could be secured easily in the following manner. The oxidation mixture from 10 g of dihydrocasimiroedine, 11 g of periodic acid and 150 cm³ of water was adjusted to pH 1·8 after 4 hr at room temperature and was then extracted continuously overnight with chloroform. Evaporation of the extract furnished 0·43 g of reddish oil which was discarded. The pH of the aqueous solution was adjusted to 5·5 with 1 N sodium hydroxide and again extracted continuously with chloroform. Drying and evaporation of the organic layer provided 5·7 g of amorphous solid which was filtered in chloroform–methanol solution through alumina before being submitted to analysis; $[\alpha]$ −3° (*c*, 0·70 in $CHCl_3$), −5° (*c*, 0·85 in 1% HCl), −14° (*c*, 0·91 in 1% NaOH).

Anal. Found: C, 61·24; H, 7·06; N, 10·46; O, 20·68.

Isolation of N-*dihydrocinnamoyl*-N-*methylhistamine* (IV). When the zinc–acetic acid treatment of the periodic acid oxidation product (III) was conducted at 60°, chromatography gave in addition to pure III about 8–10 per cent of material which could be crystallized from methanol–ether to give colorless crystals of m.p. 134–135°, $\lambda_{max}^{CHCl_3}$ 6·10 μ, pK'_a 6·5 (33% DMF), mol. wt. 240 ± 20 (by electrometric titration). The yield could not be improved on raising the reaction temperature or extending the time.

Anal. Calcd. for $C_{15}H_{19}N_3O$: C, 70·00; H, 7·44; N, 16·33; O, 6·22. Found: C, 69·69; H, 7·43; N, 16·14; O, 6·69.

Isolation of N-*methylhistamine* (V) *and di-β-*(4-*ethylimidazolyl*)-*methylamine* (VI). A solution of 5·7 g of III in 80 cm³ of 10% aqueous barium hydroxide (octahydrate) was heated under reflux for 24 hr. After removal of some insoluble material, the clear, colorless solution was saturated with carbon dioxide, the precipitated barium carbonate was collected and the filtrate was acidified with hydrochloric acid. Extraction with ether furnished 2·06 g of dihydrocinnamic acid, m.p. 40–42°, while addition of a methanolic picric acid solution to the aqueous filtrate led to a yellow picrate. Trituration with hot methanol and filtration left 300 mg of insoluble picrate (m.p. 220°), which after four recrystallizations from acetone exhibited m.p. 226–228° (dec.) and which was identified as the tripicrate of di-β-(4-ethylimidazolyl)-methylamine (VI)* by mixture melting point determination and infrared comparison with a synthetic specimen.

Anal. Calcd. for $C_{29}H_{26}N_{14}O_{21}$: C, 38·42; H, 2·89; N, 21·63; O, 37·06. Found: C, 38·10; H, 2·90; N, 21·86; O, 37·68.

Cooling of the hot methanol washes of the crude picrate led to 1·5 g of crystals, m.p. 180–187°, which were purified most effectively by chromatography, since Merck acid-washed alumina did not decompose the picrate. A 1·0 g sample of the picrate was chromatographed on 30 g of alumina and eluted with acetone and with methanol–water (9 : 1) to give 0·92 g of material with m.p. 185–188°. The analytical sample was recrystallized from methanol whereupon it exhibited m.p. 187–188°, undepressed upon admixture with a synthetic specimen of the dipicrate of N-methylhistamine (V); the infrared spectra in Nujol mull were also identical. The same dipicrate (135 mg, m.p. 188–189°) was isolated when 320 mg of IV was treated with barium hydroxide in the above described fashion.

* The hydrochloride, m.p. 231–234°, was hygroscopic and was not submitted for analysis. However, it did not give a melting point depression when mixed with a synthetic sample of the hydrochloride.

Anal. Calcd. for $C_{18}H_{17}N_9O_{14}$: C, 37·06; H, 2·94; N, 21·61; O, 38·39; N–CH_3, 2·56; mol. wt., 583·4. Found: C, 37·42; H, 3·06; N, 21·86; O, 37·60; N–CH_3, 2·01; neut. equiv. (perchloric acid titration), 283.

Alternatively, 1·45 g of III was heated under reflux for 20 hr with 1 : 1 aqueous hydrochloric acid and ether extraction removed 0·76 g of dihydrocinnamic acid. Evaporation of the aqueous solution to dryness gave a gummy hydrochloride which was treated in aqueous solution with picric acid. A brown, oily picrate was formed which yielded after repeated treatment with hot methanol 0·3 g of yellow picrate, m.p. 180–188°. The free base was regenerated by passing an acetone solution (containing a few drops of water which increased the solubility of the salt) of the picrate through a column of basic IRA–400 Amberlite resin and eluting rapidly with methanol to avoid base-catalyzed condensation of acetone. Evaporation of the eluates to dryness led to N-methylhistamine (V) as a colorless, odorless, viscous oil which was distilled twice at 0·005 mm and a bath temperature of 170°. The oil showed no selective ultraviolet absorption above 220 mμ but exhibited a blue fluorescence when exposed to an ultraviolet lamp very similar to 4-methylimidazole (prepared from the picrate which was kindly provided by Dr. C. F. Huebner of Ciba Pharmaceutical Products, Inc., Summit, New Jersey). Considerable similarities were also observed in the infrared spectra of 4-methylimidazole and N-methylhistamine.

Anal. Calcd. for $C_6H_{11}N_3$: C, 57·57; H, 8·86. Found: C, 57·58; H, 8·28; C–CH_3, 0·52.*

Treatment of 58 mg of the base with 140 mg of picric acid in methanol solution yielded 108 mg of N-methylhistamine dipicrate, m.p. 187–189°.

Anal. Calcd. for $C_{18}H_{17}N_9O_{14}$: C, 37·06; H, 2·94; N, 21·61. Found: C, 37·37; H, 2·86; N, 21·66.

When a solution of 115 mg of styphnic acid in 3 cm^3 of methanol was added to 45 mg of N-methylhistamine (V) dissolved in 2 cm^3 of the same solvent, an immediate precipitate of the monostyphnate of N-methylhistamine separated. The substance was very insoluble in methanol and had to be recrystallized from acetone–methanol, whereupon it exhibited m.p. 235–245° (very dependent upon rate of heating).

Anal. Calcd. for $C_{12}H_{14}N_6O_8$: C, 38·92; H, 3·81; N, 22·70. Found: C, 38·87; H, 4·17; N, 22·99.

Monostyphnate formation (in contrast to the above described dipicrate) was clearly due to the insolubility of the salt in methanol and a distyphnate could indeed be prepared when the base and styphnic acid were mixed in water solution and then recrystallized from ethanol; yellow needles, m.p. 203–204°.

Anal. Calcd. for $C_{18}H_{17}N_9O_{16}$: C, 35·13; H, 2·79; N, 20·50. Found: C, 34·97; H, 2·74; N, 20·87.

Synthesis of N-*methylhistamine* (V) *and di-*β*-(4-ethylimidazolyl)-methylamine* (VI). A solution of 2·0 g of 4-(β-chloroethyl)-imidazole hydrochloride, prepared from butyne-1, 4-diol according to the procedure of Huebner,[6] in 20 cm^3 of 10% methanolic methylamine was heated in a sealed tube for 15 hr at 95–100°. The contents were cooled, evaporated to dryness *in vacuo*, taken up in a small amount of water and treated with a methanolic solution of 0·62 g of picric acid. The picrate was crystallized from a large amount of methanol and three crops were collected: (a) 252 mg, m.p.

* In order to observe the ease of C-methyl determination in the imidazole series, a sample of 4-methylimidazole was submitted to Kuhn-Roth analysis and yielded 15·5 per cent C–CH_3 (calcd., 18·3 per cent).

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200–210°; (b) 86 mg, m.p. 181–215°; (c) 172 mg, m.p. 177–179°. Several recrystallizations of the first crop from acetone raised the m.p. of di-β-(4-ethylimidazolyl)-methylamine tripicrate (VI) to 225–227°.

Anal. Calcd. for $C_{29}H_{26}N_{14}O_{21}$: C, 38·42; H, 2·89. Found: C, 38·63; H, 3·17.

The hydrochloride, m.p. 233–235°, was hygroscopic and was not analyzed.

Recrystallization of the third picrate crop from methanol yielded N-methylhistamine dipicrate, m.p. 187–189° (in reference 5, m.p. 188°).

Anal. Calcd. for $C_{18}H_{17}N_9O_{14}$: C, 37·06; H, 2·94; O, 38·39. Found: C, 37·40; H, 3·20; O, 38·57.

Tetrahedron, 1958, Vol. 2, pp. 173–182. Pergamon Press Ltd., London

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ALKALOIDS FROM *STEMMADENIA* SPECIES—I*

THE ALKALOIDS OF *S. Donnell-Smithii* AND *S. Galeottiana* †

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Abstract—From *Stemmadenia Donnell-Smithii* and *S. Galeottiana*, the following new alkaloids were isolated: (+)-quebrachamine (IV), an optical isomer of the known (−)-quebrachamine; *iso*voacangine (IIIa), a position isomer of voacangine, and stemmadenine. In addition, the following known alkaloids were also found: voacangine (Ia), voacamine, tabernanthine (IIIb) and ibogamine.

IN view of the great current interest in alkaloids of the *Apocynaceae* family, we undertook a study of some species of the genus *Stemmadenia* belonging to the same family.

We wish to report here the results obtained with *Stemmadenia Donnell-Smithii* and *S. Galeottiana*, two species growing in the tropical jungle of Mexico. The two were collected by the authors§ in the State of Veracruz and represent trees 5–10 m high.

Stemmadenia Donnell-Smithii (Rose) Woodson

From this tree the following alkaloids were obtained:

Voacangine (Ia), described by Janot and Goutarel,[1] who first isolated it from *Voacanga africana;* its structure was established by Taylor.[2]

(+)-*Quebrachamine* an optical isomer of the well-known quebrachamine, showing the same constants and empirical formula but with the opposite rotation. The proof that it is the mirror image was obtained by determination of the optical rotation dispersion,‖ as shown in Fig. 1. By mixing equal amounts of the two isomers and crystallising them from alcohol, the pure racemate was obtained. We propose, therefore, the name (+)-*quebrachamine* for our isomer and the name (−)-*quebrachamine* for the previously known alkaloid.[3–6]

iso*Voacangine* IIIa proved to be a new isomer of voacangine with the difference that the methoxyl group, which in voacangine is attached to position 5 of the indole ring, is located at C-6 in the new isomer. By decarboxylation of it, tabernanthine[7] (IIIb) was obtained, whose structure was established by Taylor.[2]

Tabernanthine (IIIb), identical with the alkaloid described by Delourme-Houdé,[7] and *Voacamine*. The constants of our alkaloid seem to coincide with those reported

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† Taken from a D.Sc. thesis of F. Walls.
‡ Fellow of the Instituto Nacional de la Investigación Científica.
§ We wish to thank Dr. F. Miranda of the Instituto de Biología de la Universidad Nacional Autónoma de México, for his assistance in localisation and classification of the species.
‖ We wish to thank Dr. J. S. E. Holker of Wayne State University, Detroit, Mich., who carried out these determinations.

[1] M. M. Janot and R. Goutarel *C. R. Acad. Sci., Paris* **240**, 1800 (1955).
[2] W. I. Taylor *J. Amer. Chem. Soc.* **79**, 3298 (1957).
[3] O. Hesse *Liebigs Ann.* **211**, 249 (1882).
[4] E. Field *J. Chem. Soc.* **125**, 1444 (1924).
[5] E. Schlittler and E. Gellért *Helv. Chim. Acta* **34**, 920 (1951); E. Gellért and B. Witkop *Helv. Chim. Acta* **35**, 114 (1952).
[6] O. O. Orazi, R. A. Corral, J. S. E. Holker and C. Djerassi *J. Org. Chem.* **21**, 979 (1956).
[7] J. Delourme-Houdé *Ann. Pharm. France* **4**, 30 (1946); *Chem. Abstr.* **41**, 1390[d] (1947).

by Janot and Goutarel,[8] except that our analytical results correspond to $C_{34}H_{39}O_4N_3$ rather than $C_{42}H_{52}O_5N_4$[9] or $C_{45}H_{56}O_6N_4$[9].

Stemmadenine, a new alkaloid with an empirical formula $C_{21}H_{26-28}O_3N_2$, whose structure elucidation is currently in progress.

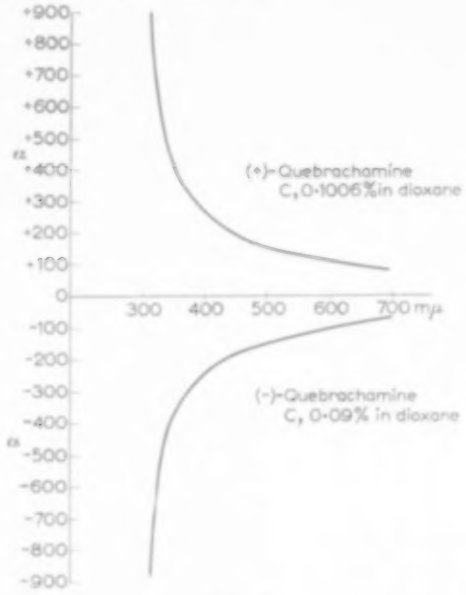

FIG. 1.

The only alkaloid isolated from *Stemmadenia Galeottiana* (*A. Rich.*) *Miers*, in appreciable amount was the known alkaloid *ibogamine* described by Janot *et al.*,[10] whose structure was also proved by Taylor.[2]

Before the structure of these alkaloids were announced by Taylor, several degradation experiments were carried out, and we wish to report here those which do not duplicate the already published ones.*

Voacangine (Ia). The selenium dehydrogenation produced ibogaine (Ib),[11] which had been obtained previously by saponification and decarboxylation of voacangine (Ia).

The ozonisation of voacangine (Ia) furnished a yellow compound —$C_{22}H_{28}O_5N_2$ (IIa)—, which is presumed to be the product of oxidative fission of the indole double-bond. It was not possible to decarboxylate this compound (IIa) as is the case with the parent alkaloid, since the acid (IIb) which could be isolated and which upon methylation with diazomethane regenerates compound (IIa), is completely destroyed when heated with aqueous hydrochloric acid. However, the ozonisation product (IIa) produced the 3-methyl-5-ethyl-pyridine, when dehydrogenated with palladium–charcoal.

* At the time this work was done, the structure of voacangine had not been established. We wish to thank Profs. V. Prelog, H. C. Brown, Takeo Ishiguro, E. R. Wallsgrove and H. L. Lochte, who supplied us with samples of substituted pyridines to compare with our degradation products.

[8] M. M. Janot and R. Goutarel *C. R. Acad. Sci., Paris* **240,** 1719 (1955).

[9] Physical Data of Indole and Dihydroindole Alkaloids. Lilly Research Laboratories, Indianapolis 6, Indiana, U.S.A.

[10] M. M. Janot, R. Goutarel and R. P. A. Sneeden *Helv. Chim. Acta* **34,** 1205 (1953).

[11] M. M. Janot and R. Goutarel *C.R. Acad. Sci., Paris* **241,** 986 (1955).

The reduction with lithium aluminium hydride of voacangine (Ia), produced the alcohol *voacanginol* (Ic) $C_{21}H_{28}O_2N_2$, which upon ozonisation led to a similar scission product corresponding to $C_{21}H_{28}O_4N_2$ (IIc).

TABLE 1. ABSORPTION SPECTRA OF SUBSTITUTED INDOLES DETERMINED IN A BECKMAN DK-2 SPECTROPHOTOMETER

	mμ	ε
(+)-Quebrachamine	228, 284, 291	32,820; 7650; 7290
Indole	217, 263, 270, 279, 287	36,450; 4050; 4520; 4370; 3400
2-Methyl-indole[13]	220, 270, 288	32,400; 7770; 5030
3-Methyl-indole[14]	223, 281, 290	32,400; 6310; 5500
2,3-Dimethyl-indole[15]	227, 283, 290	36,400; 8130; 7250
2,3-*Cyclo*pentene-indole[16]	229, 280	26,750; 5070
1,2,3,4-Tetrahydrocarbazole[17]	227, 282, 290	53,100; 9500; 8460
2,3-*Cyclo*heptene-indole[18]	228, 284, 291	25,020; 7460; 6840
3-[N-piperidil-methyl]-indole[19]	215, 269–277, 279, 286	55,280; 8650; 8770; 7570
2-Methyl-3-[N-piperidil-methyl]-indole[20]	220, 270–280, 287	58,410; 9790; 8100

With cyanogen bromide, voacangine (Ia) gives three different products. Two of them were isomers with formulae $C_{23}H_{28}O_3N_2Br$, while the third had a formula $C_{23}H_{27}O_3N_2$. When one of the two isomers, obtained as main product, was treated with Raney nickel, it produced 2 new compounds: $C_{23}H_{30}O_4N_2$, which seems to be an aldehyde, and the other one $C_{23}H_{31}O_3N_2$, which seems to be an amine obtained by the reduction of the nitrile moiety, but their structures were not further investigated.

(+)-*Quebrachamine* (IV). By functional group analysis, evidence was obtained of the presence of one N-methyl grouping. By comparison (see Table 1) of its ultra-violet spectrum with those of different synthetic indoles, we have come to the conclusion that (+)-quebrachamine is an α,β-disubstituted indole. Although it was not possible to obtain recognisable degradation products, it has been reported by Witkop[12] that (−)-quebrachamine gives, by degradation, 3,5-diethylpyridine. Taking these facts into consideration, we are proposing the following partial structure (IV) for (+)-quebrachamine, which differs significantly from that proposed by Witkop[12] in that no free α-indole position is present.

(+)-Quebrachamine reacts with cyanogen bromide by addition of the CN grouping to the double bond of the indole, giving a compound $C_{20}H_{25}N_3$, whose ultra-violet absorption spectrum points to an indolenine. By hydrolysis of the latter with potassium hydroxide, the original (+)-quebrachamine was recovered. Therefore it is assumed that the addition compound has structure V.

[12] B. Witkop *J. Amer. Chem. Soc.* **79**, 3193 (1957).
[13] *Beilstein* Vol. XX, p. 311.
[14] *Beilstein* Vol. XX, p. 315.
[15] *Beilstein* Vol. XX, p. 319.
[16] W. H. Perkin and P. Plant *J. Chem. Soc.* **123**, 3242 (1923).
[17] *Beilstein* Vol. XX, II, p. 257.
[18] W. H. Perkin, S. Glennand and P. Plant *J. Chem. Soc.* 2583 (1928).
[19] H. Kuhn and O. Stein *Ber. Dtsch. Chem. Ges.* **70**, 567 (1937).
[20] W. J. Brehn and H. G. Lindwall *J. Org. Chem.* **15**, 685 (1950).

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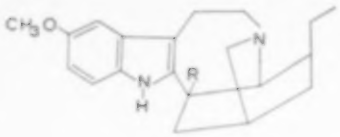
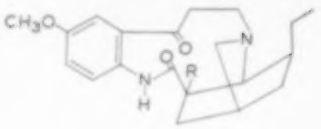


I a, R=COOCH$_3$
b, R=H
c, R=CH$_2$—OH



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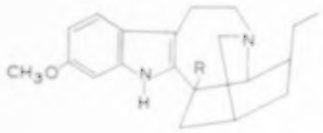
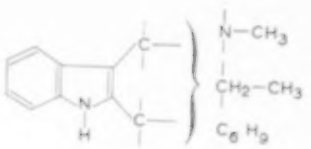
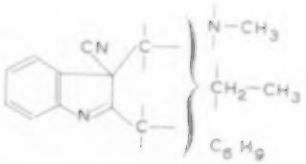
b, R=COOH
c, R=CH$_2$—OH



III a, R=COOCH$_3$
b, R=H



IV



V

EXPERIMENTAL*

Both *Stemmadenias* were collected in the tropical jungle of the State of Veracruz, near the road leading from Catemaco to Montepio.

Stemmadenia Donnell-Smithii

(*A*) *Wood*

A trunk of about 40 cm in diameter and weighing about 100 kg was cut into small pieces, ground to a powder in a Mikro-Pulverizer 1-W mill and dried at 37°. As a typical example, a 11·5 kg portion was continuously extracted with ethanol. The concentrated extract was evaporated to 1·5 l. and 2 l. of 5% HCl were added. The precipitate that formed was filtered off and the solution was extracted with ether. The aqueous acid phase was made alkaline with conc. NaOH, adding ice to avoid overheating, and then it was extracted with ether. The ethereal fraction was washed with water, dried and evaporated under vacuum. The residue (35 g) was dissolved in benzene and chromatographed on 1·5 kg of activated alumina, collecting fractions of 300 cc. In the first three fractions, eluted with benzene, 21 g of crude voacangine was obtained.

From fractions 7–8 (benzene–1% MeOH), 0·22 g was obtained of an alkaloid

* All melting points were determined with a Kofler block. Optical rotations were determined in chloroform unless otherwise stated. Ultra-violet spectra were measured in 96% ethanol in a Beckman DK-2 spectrophotometer and infra-red spectra, in chloroform solution, in a Perkin-Elmer Model 21 double-beam spectrophotometer. The microanalyses were carried out by Dr. F. Pascher, Bonn, Germany, and Mr. J. F. Alicino, Metuchen, N. J. As adsorbents, Harshaw Chemical Co. Activated alumina or Alcoa grade F-20 alumina were used.

which showed m.p. 233–235° (dec.) after three recrystallisations from ether–methanol. It has not been investigated further.

From fractions 11–13 (benzene–3% MeOH), 0·30 g of another alkaloid was obtained, which after recrystallisation from ether–methanol showed m.p. 135–139°. It similarly has not been investigated further.

Voacangine. The 21 g of crude voacangine were recrystallised from ether–methanol until a sharp melting point was reached, yielding 11·2 g, which showed m.p. 137–138°; $[\alpha]_D^{25}$ −28°; λ_{max} 224, 288 mμ; ε, 32,580; 10,220; λ_{max} 5·83 μ.

The comparison of this sample with one of authentic voacangine* did not show depression of the mixture melting point, and the infra-red curves were identical.

(Found: C, 71·60; H, 7·58; O, 13·39; N, 7·52. Calc. for $C_{22}H_{28}O_3N_2$: C, 71·71; H, 7·66; O, 13·03; N, 7·60%).

It gives a picrate which shows m.p. 148° (dec.) from methanol.

(Found: C, 56·42; H, 5·49; O, 26·74; N, 11·73. Calc. for $C_{28}H_{31}O_{10}N_5$: C, 56·27; H, 5·23; O, 26·78; N, 11·72%).

Degradation of voacangine. (a) With palladium: A mixture of 0·5 g of voacangine and 1·0 g of 5% palladium–charcoal was heated at 220° for 45 min. The volatile fraction was condensed and at the end of the reaction it was dissolved in methanol and treated with a methanolic solution of picric acid. The picrate was filtered and crystallised from acetone (0·09 g) and showed m.p. 181–182°. The m.p. was undepressed when mixed with the picrate of an authentic sample of 3-methyl-5-ethyl pyridine, (m.p. 181–182°).†

(Found: C, 48·63; H, 4·12; O, 31·50; N, 15·95. Calc. for $C_{14}H_{14}O_7N_4$: C, 48·00; H, 4·03; O, 31·97; N, 16·00%).

From the picrate, the free base was obtained, which was an oil with λ_{max} 262, 268, 274; ε, 2780; 3230; 2600.

The non-volatile fraction of the degradation was extracted with benzene, the palladium–charcoal was filtered off and the residue was chromatographed on 50 g of alumina F-20. From the fraction eluted with ether, a residue was obtained which was purified by sublimation at 90° and 0·01 mm, giving a crystalline sublimate with m.p. 80–81°; λ_{max} 228, 285; ε, 24,580; 7020.

(Found: C, 69·14; H, 7·50; O, 16·37; N, 7·03. Calc. for $C_{11}H_{13}O_2N$: C, 69·09; H, 6·85; O, 16·73; N, 7·33. Calc. for $C_{23}H_{30}O_4N_2$: C, 69·32; H, 7·59; O, 16·06; N, 7·03%).

It has not been possible to identify this compound until now. In the infra-red it does not show a carbonyl band and therefore there is no explanation as to why there are 2 or 4 oxygens in the molecule. The ultra-violet spectrum seems to correspond to a 5-methoxy-2,3-disubstituted indole (Table 2).

(b) With selenium: A mixture of 1 g of voacangine and 2·5 g of selenium was heated for 1 hr at 220°. The residue was extracted with benzene and the solution was chromatographed on 50 g of alumina F-20, collecting fractions of 50 cc. Fractions 12–15 (100 per cent ether) gave 0·12 g of a crystalline product, that, after recrystallisation from methanol, gave m.p. 150–151°; $[\alpha]_D^{25}$ −56° (alcohol); λ_{max} 227, 293 mμ; ε, 27,800; 7190.

* We wish to thank Prof. M. M. Janot from the Faculté de Pharmacie de Paris for supplying us with a sample of his voacangine.

† We wish to thank Prof. H. L. Lochte from the University of Texas for supplying us with this authentic sample.

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TABLE 2

5-Methoxy-1,2,3,4-tetrahydrocarbazole[24]	λ_{max} 227, 273, 293 mμ; ε, 35,000; 7600; 7400
6-Methoxy-1,2,3,4-tetrahydrocarbazole[24]	λ_{max} 229, 270, 300 mμ; ε, 33,000; 4500; 5100
7-Methoxy-1,2,3,4-tetrahydrocarbazole[24]	λ_{max} 226, 271; ε, 42,000; 7050
2,3-Dimethyl-6-methoxyindole[25]	λ_{max} 228, 273, 298; ε, 32,400; 4790; 5500
*iso*Voacangine (6-methoxy)	λ_{max} 227, 278, 300; ε, 35,650; 4580; 6540
$C_{12}H_{13}ON$ (6-methoxy) (obtained by dehydrogenation of *iso*voacangine)	λ_{max} 228, 273, 298; ε, 35,830; 2360; 2720
Voacangine (5-methoxy)	λ_{max} 224, 288; ε, 32,580; 10,220
$C_{11}H_{13}O_2N$ (obtained by dehydrogenation of voacangine)	λ_{max} 228, 285; ε, 24,580; 7020

(Found: C, 77·01; H, 8·47; O, 5·40; N, 9·23. Calc. for $C_{20}H_{26}ON_2$: C, 77·30; H, 8·44; O, 5·31; N, 9·03%).

These constants coincide with those reported for ibogaine:[21,22] m.p. 150°; $[\alpha]_D^{25}$ −53° (alcohol); λ_{max} 226, 298 mμ; ε, 24,400; 8590 and a formula $C_{20}H_{26}ON_2$.

Ozonization of voacangine. Isolation of II(a). Following Karrer's directions,[23] the equivalent of 1·3 moles of ozone was bubbled through a solution of 3 g of voacangine in 60 ml of acetic acid and 22·5 ml of water, cooled externally with ice. The resulting solution, deep-red in colour, was basified with conc. NaOH and the precipitate was filtered off (3 g). This was dissolved in benzene and chromatographed on 150 g of alumina. From the benzene eluates, 1·08 g of yellow crystals were obtained, which exhibited m.p. 160–163°. By recrystallisation from chloroform–methanol, 0·96 g (30·1 per cent) of analytical sample (II) was obtained, m.p. 186–187°; $[\alpha]_D^{25}$ +136°; λ_{max} 270, 384 mμ; ε, 8640; 17,760; λ_{max} 5·83, 5·93, 6·0, 6·5 μ.

(Found: C, 65·75; H, 7·01; O, 20·34; N, 6·98. Calc. for $C_{22}H_{28}O_5N_2$: C, 65·98; H, 7·05; O, 19·98; N, 7·00%).

Compound (IIa) (0·3 g) was saponified with 0·6 g of potassium hydroxide in 60 ml of methanol by boiling for 8 hr. The alcohol was then evaporated, water was added and it was acidified with HCl to congo-red. The solution was extracted with chloroform. After the usual work-up, 0·18 g of a yellow solid acid was obtained which could not be crystallised. It was dissolved in methanol and esterified with diazomethane. After 30 min it was evaporated to dryness. The resulting crystalline residue showed the same m.p. as the original compound (IIa) and the mixture m.p. was not altered.

Compound IIa (0·5 g) was dehydrogenated with 1 g of 5% palladium–charcoal by heating the mixture for 1 hr at 250°. The volatile fraction was collected and a picrate (0·01 g m.p. 181–182°) was obtained from methanol. The mixture with an authentic picrate of 3-methyl-5-ethyl pyridine did not depress the melting point.

Compound IIa did not give any recognisable degradation products when it was treated with $LiAlH_4$; $NaBH_4$; KOH in ethylene-glycol, etc.

Voacanginol (Ic). To 1·0 g of voacangine (Ia) in 25 ml of anhydrous tetrahydrofuran,

[21] J. Dybowski and E. Landrin *C. R. Acad. Sci., Paris* **133,** 748 (1901).
[22] M. Raymond-Hamet *Bull. Soc. Chim. France* **9,** 620 (1942).
[23] P. Karrer and P. Enslin *Helv. Chim. Acta* **32,** 1390 (1949).
[24] J. R. Chalmers, H. T. Openshaw and G. F. Smith *J. Chem. Soc.* 1115, (1957).
[25] N. Neuss, H. E. Boaz and J. W. Forbes *J. Amer. Chem. Soc.* **76,** 2463 (1954).

1 g of $LiAlH_4$ in 25 ml of anhydrous tetrahydrofuran was added. It was boiled for 4 hr and then worked up in the usual way. From the chromatography of the residue, the fractions obtained with ether and ether–10% chloroform gave 0·570 g of crystals with m.p. 203–205°; λ_{max} 228, 292 mμ; ε, 20,300; 5660; λ_{max} 3·0 μ.

(Found: C, 74·27; H, 8·61; O, 9·27; N, 8·14. Calc. for $C_{21}H_{28}O_2N_2$: C, 74·08; H, 8·29; O, 9·40; N, 8·23%).

Voacanginol gives a hydrochloride that crystallises only if acetone is added, showing then, m.p. 202–204° (dec.); $[\alpha]_D^{25}$ ±0° (water); λ_{max} 211, 228, 292 mμ; ε, 27,360; 26,650; 9660; λ_{max} 3·2, 5·85 μ (Nujol).

(Found: C, 67·08; H, 8·09; O, 9·59; N, 6·66; Cl, 8·68. Calc. for $C_{21}H_{28}O_2N_2$—HCl—C_3H_6O: C, 66·26; H, 8·11; O, 11·03; N, 6·44; Cl, 8·15%).

When the crystals are boiled several times with methanol, and then evaporated to dryness, an oily residue is obtained that does not show the maximum at 5·85 μ due to the acetone.

Voacanginol (1·8 g) was ozonised in 40 ml of acetic acid and 20 ml of water with 1·3 moles of ozone. The reddish solution was alkalinised with NaOH, extracted with ether and the red residue was chromatographed on 50 g of alumina. The eluate of benzene–ether (9 : 1) afforded 0·4 g of crystals with m.p. 124–125°. After recrystallisation from acetone–hexane, the m.p. was 130–131°; $[\alpha]_D^{25}$ +72°; λ_{max} 275, 395 mμ; ε, 18,140; 22,920; λ_{max} 3·05, 5·9, 6·15 μ.

(Found: C, 67·88; H, 7·73; O, 16·68; N, 8·23. Calc. for $C_{21}H_{28}O_1N_2$: C, 67·72; H, 7·58; O, 17·18; N, 7·52%).

von Braun degradation of voacangine (Ia). A mixture of 10 g of voacangine (Ia), 20 g of freshly prepared cyanogen bromide and 150 ml of chloroform, was boiled for 9 hr, and let stand at room temperature overnight. The chloroform and the excess of BrCN were evaporated. The residue crystallised from ether, affording 9·45 g of a product with m.p. 198–200°. By recrystallisation from chloroform–methanol and acetone–methanol, 5.26 g of analytical sample of compound A were obtained which showed m.p. 203–204°; $[\alpha]_D^{18}$ −92°; λ_{max} 218, 285 mμ; ε, 29,140; 10,810; λ_{max} 3·13, 4·59, 5·82 μ.

(Found: C, 58·89; H, 5·98; O, 10·67; N, 8·95; Br, 16·71. Calc. for $C_{23}H_{28}O_3N_3Br$: C, 58·22; H, 5·96; O, 10·11; N, 8·85; Br, 16·84%).

By chromatography of the mother liquors, 3 g more of compound A were obtained plus very small amounts of 2 other crystalline compounds:

Compound B (370 mg) m.p. 238–240°; $[\alpha]_D^{25}$ +46°; λ_{max} 221, 284 mμ; ε, 28,200; 9470; λ_{max} 2·95, 4·58, 5·81 μ.

(Found: C, 58·59; H, 5·96; O, 10·41; N, 8·76; Br, 17·01. Calc. for $C_{23}H_{28}O_3N_3Br$: C, 58·21; H, 5·96; O, 10·11; N, 8·85; Br, 16·84%).

Compound C (100 mg) m.p. 175–176°; $[\alpha]_D^{25}$ −34°; λ_{max} 233, 284 mμ; ε, 12,800; 7300; λ_{max} 4·57, 5·81 μ.

(Found: C, 70·50; H, 6·84; O, 12·23; N, 10·65. Calc. for $C_{23}H_{27}O_3N_3$: C,70·20; H, 6·92; O, 12·20; N, 10·68%).

This compound seems to be an indolenine. The reduction of compound A (1·5 g) by boiling it for 3 hr with 3 g of Raney nickel in 100 ml of ethanol, produced 0·45 g of a compound with m.p. 230–233°. By recrystallisation, an analytical sample was obtained which showed m.p. 240–241°; $[\alpha]_D^{25}$ ±0°; λ_{max} 218, 284mμ; ε, 37,200; 20,000; λ_{max} 5·80 μ.

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(Found: C, 69·51; H, 7·43; O, 15·94; N, 7·43. Calc. for $C_{23}H_{30}O_4N_2$: C, 69·32; H, 7·59; O, 16·06; N, 7·03%).

This compound is probably an aldehyde produced by the transformation of the nitrile group.

By chromatography of the mother liquors another compound (0·16 g) was obtained which showed m.p. 200°. The recrystallisation from chloroform–ethanol afforded an analytical sample with m.p. 212°; $[\alpha]_D^{25}$ −215°; λ_{max} 212, 285 mμ; ε, 38,750; 15,500; λ_{max} 3·2, 5·81, 6·2 μ.

(Found: C, 69·71; H, 7·92; O, 12·27; N, 10·27. Calc. for $C_{23}H_{31}O_3N_3$: C, 69·49; H, 7·86; O, 12·08; N, 10·57%).

This product is probably an amine produced by the reduction of the nitrile.

(*B*) *Bark*

50 kg of bark were pulverised in a Mikro-Pulverizer 1-W mill and the powder was dried at 30°; 35 kg of dried material were obtained, which were continuously extracted with alcohol in a pilot plant. The extract was concentrated to 4 l., and with continuous agitation 10 l. of 5% aqueous hydrochloric acid were added. The precipitate was filtered off and discarded. The filtrate was made alkaline with a solution of sodium–hydroxide, and the precipitate was filtered, washed, and dried, producing 240 g of solids. By extraction of this powder with benzene, 55 g of an oil was obtained and this was chromatographed on 2·5 kg of alumina. In the first 4 fractions (benzene–hexane 1 : 1), 6 g of crude (+)-quebrachamine m.p. 133–137° were obtained. From the rest of the fractions, 35 g of oil were isolated, which on rechromatography gave *tabernanthine*, iso*voacangine* and *voacamine*.

The recrystallisation from hexane and then from methanol of the crude (+)-quebrachamine, followed by sublimation at 130° and 0·001 mm, afforded 3 g of pure (+)-quebrachamine, m.p. 147–149°; $[\alpha]_D^{25}$ +111°; λ_{max} 228, 284, 291 mμ; ε, 32,820; 7650; 7290; λ_{max} 2·95 μ. The infra-red spectra of (+)- and (−)-quebrachamines were identical.

(Found: C, 81·01; H, 9·63; N, 9·81; Calc. for $C_{19}H_{26}N_2$: C, 80·80; H, 9·28; N, 9·92%). (Found: 1·4. Calc. for one C—CH_3, 5·3%). (Found: 2·73. Calc. for one N—CH_3, 5·3%*).

By mixing equal amounts of (+)- and (−)-quebrachamines and crystallising from aqueous methanol, the racemate was obtained, which showed m.p. 112–115°; $[\alpha]_D^{20}$ ±0·00°.†

(+)-quebrachamine (IV) gives a bright red picrate which shows m.p. 190–193°. By mixing equal amounts of it with (−)-quebrachamine picrate and recrystallising from methanol, a product with m.p. 176–179°; $[\alpha]_D^{20}$ ±0·00° was obtained.†

To 1·7 g of (+)-quebrachamine (IV) in 20 ml of chloroform, a solution of 5 g of cyanogen bromide in 60 ml of chloroform was added and the mixture was boiled for 4 hr. At this time the solution was deep-red. The solvent and the excess of BrCN were evaporated under vacuum and the residue, dissolved in chloroform, was chromatographed on 170 g of alumina F-20. From the chloroform–2% methanol fractions, 0·173 g of a product m.p. 105–110° was obtained. It was purified by

* A N—CH_3 determination on (−)-quebrachamine, kindly supplied by Dr. C. Djerassi, from Syntex, S.A., Mexico City, gave a value of 3·11.

† We wish to thank Dr. J. S. E. Holker from Wayne State University, Detroit, Michigan, for preparing these racemates.

sublimation at 95° and 0·001 mm showing m.p. 111–112°; λ_{max} 224, 286 mμ; ε, 18,000; 8460; λ_{max} 4·52 μ.

(Found: C, 78·27; H, 8·17; N, 13·66; MW, (Rast) 289. Calc. for $C_{20}H_{25}N_3$: C, 78·13; H, 8·20; N, 13·67%; MW, 307).

When 0·11 g of this compound was refluxed for 2 hr with 10 ml of 10% potassium hydroxide in ethanol, and then left standing at room temperature overnight, 0·075 g of crystals was obtained. By recrystallisation from chloroform–methanol they showed m.p. 143–144°, and after sublimation at 130° and 0·001 mm the m.p. was 147–149°; λ_{max} 226, 283, 290 mμ; ε, 37,860; 10,840; 10,270; λ_{max} 2·95 μ. The mixture melting point with (+)-quebrachamine was undepressed and the infra-red spectra were identical.

Rechromatography of the 35 g of oil on 1 kg of activated alumina gave, in the fractions eluted with benzene–hexane (50:50), 4·2 g of oil from which *tabernanthine* was crystallised out; from the fractions obtained by elution with benzene–hexane (80 : 20), 5·38 g of oil were obtained, from which iso*voacangine* was isolated; finally, from the fractions eluted with benzene–ether (1 : 1), 2·7 g of oil were obtained from which *voacamine* was isolated.

Tabernanthine. The 4·2 g of oil were crystallised from benzene–hexane, obtaining 400 mg of crude *tabernanthine*, m.p. 203–208°. By recrystallisation and sublimation at 160° and 0·005 mm, 204 mg of analytical sample were obtained which showed m.p. 211–212°; $[\alpha]_D^{25}$ −35°; λ_{max} 229, 271, 299 mμ; ε, 35,970; 4410; 5810.

(Found: C, 77·63; H, 8·57; O, 5·17; N, 9·18; O—CH_3, 10·35. Calc. for $C_{20}H_{26}ON_2$: C, 77·38; H, 8·44; O, 5·15; N, 9·03%; O—CH_3, 10·00).

The mixture melting point with an authentic sample of tabernanthine, obtained by decarboxylation of *iso*voacangine, was undepressed and the infra-red spectra were identical.

iso*Voacangine*. The oil (5·38 g) obtained from the chromatogram was crystallised from ether–methanol giving 1·45 g of crude *iso*voacangine, m.p. 148–149°, which after sublimation (140° and 0·01 mm) gave 1·2 g of pure *iso*voacangine m.p. 156–157°; $[\alpha]_D^{22}$ −52°; λ_{max} 227, 278, 300 mμ; ε, 35,650; 4580; 6540; λ_{max} 2·96, 5·8, 6·17 μ.

(Found: C, 71·24; H, 7·71; O, 13·56; N, 7·67; OCH_3, 16·96. Calc. for $C_{22}H_{28}O_3N_2$: C, 71·71; H, 7·66; O, 13·03; N, 7·60%; 2—OCH_3, 16·86).

*iso*Voacangine gives a crystalline hydrochloride, m.p. 225–228°, from methanol.

This compound is called *iso*voacangine because it was established that it was an isomer of voacangine in which the methoxyl grouping was attached to position 6 of the indole instead of at C-5 as in voacangine, by comparison of the ultra-violet spectra (Table 2) and by decarboxylation to tabernanthine.

When 0·5 g of *iso*voacangine was saponified with 20 ml of 15% potassium hydroxide in ethanol, by boiling for 12 hr and then the solution was acidified to pH3 with HCl, an acid was obtained which on heating for ½ hr on the steam bath, underwent decarboxylation. The solution was made alkaline and extracted with ether. From the ethereal fraction, after the usual work-up, 0·26 g of tabernanthine were obtained. [Reported constants[7] are m.p. 210°; $[\alpha]_D^{25}$ −40° (acetone); λ_{max} 228, 299 mμ; ε, 33,600; 5800]. Found: m.p. 211–212°; $[\alpha]_D^{25}$ −35°; λ_{max} 226, 295 mμ; ε, 37,160; 5760.

(Found: C, 77·43; H, 8·53; O, 5·20; N, 9·08; O—CH_3, 9·98. Calc. for $C_{20}H_{26}ON_2$: C, 77·38; H, 8·44; O, 5·15; N, 9·03%; O—CH_3, 9·91).

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The dehydrogenation of 0·5 g of *iso*voacangine with 1 g of 5% palladium–charcoal, heating at 220–240° for 45 min, produced a volatile fraction which gave a picrate (0·042 g). By recrystallisation from methanol, the m.p. of the picrate was 179–182°, which was undepressed when mixed with an authentic sample of the picrate of 3-methyl 5-ethyl pyridine.

By extraction with benzene of the residue of the dehydrogenation, and chromatography on 25 g of alumina F-20, from the fractions eluted with ether, 135 mg of a semi-crystalline compound was obtained, which was sublimed three times at 65° and 0·005 mm, giving 22 mg of a crystalline product, m.p. 81–82°; λ_{max} 228, 273, 298 mμ; ε, 35,830; 2360; 2720.

(Found: C, 75·86; H, 7·95; O, 9·00; N, 7·18; O—CH_3, 16·87. Calc. for $C_{12}H_{13}ON$: C, 76·15; H, 7·99; O, 8·45; N, 7·40%; 1 O—CH_3, 16·39).

From the ultra-violet spectrum and the microanalysis, this compound seems to be a 6-methoxy-2 (or 3)-methyl-3 (or 2)-ethyl-indole.

Voacamine. From the fraction of 2·7 g of oil obtained in the chromatogram, 0·23 g crystallised out, and by further recrystallisation, there was isolated 0·14 g of pure *voacamine*, m.p. 223–224° (dec.); $[\alpha]_D^{26}$ −46°; λ_{max} 225, 286, 292; ε, 48,400; 14,860; 15,180.

(Found: C, 74·07; H, 7·58; O, 11·48; N, 7·54; O—CH_3, 12·73. Calc. for $C_{24}H_{30}O_4N_2$:* C, 73·75; H, 7·10; O, 11·56; N, 7·59%; 2 O—CH_3, 11·20).

This analysis does not check for the suggested formulae $C_{42}H_{52}O_5N_4$* or $C_{45}H_{56}O_6N_4$.[9]

The infra-red spectrum of our sample was identical with that reported for voacamine.[8]

(*C*) *Fruits*

1 kg of ground fruits of *S. Donnell-Smithii* was extracted with hot alcohol. The extract was concentrated, diluted with 1 l. of 5% acetic acid and extracted with hexane; the aqueous phase was made alkaline with NaOH and extracted with chloroform. This phase, after evaporation to dryness, left 2 g of residue, which was chromatographed on 200 g of alumina. From the fractions eluted with ether, 0·15 g of *stemmadenine* was obtained, showing m.p. 199–200° (dec.); $[\alpha]_D^{25}$ +324° (pyridine); λ_{max} 227, 284, 292 mμ; ε, 35,720; 7345; 7060; λ_{max} 3·05, 3·85 μ (nujol).

(Found: C, 70·80; H, 7·51; O, 14·09; N, 7·81. Calc. for $C_{21}H_{26}O_3N_2$: C, 71·16; H, 7·39; O, 13·54; N, 7·90%).

The structure of this alkaloid will be reported in a future paper.

Stemmadenia Galeottiana

Wood

Following the same procedure as in the case of the wood of *S. Donnell-Smithii*, from 16 kg of wood dust, 3·4 g of pure alkaloid was obtained, which showed m.p. 163–164°; $[\alpha]_D^{25}$ −60°; λ_{max} 225, 283, 291 mμ; ε, 36,180; 9130; 8710; λ_{max} 2·94 μ.

(Found: C, 81·33; H, 8·64; N, 9·91; C—CH_3, 4·34. Calc. for $C_{19}H_{24}N_2$: C, 81·38; H, 8·63; N, 9·99%; C—CH_3, 5·36).

The physical constants and the empirical formula coincide for those reported for *ibogamine*[10]: m.p. 163°; $[\alpha]_D$ −54° (ethanol).

* The calculated analysis was obtained following the method suggested by R. Krzikalla. Rechentafeln zur chemischen elementar-analyse. Verlag Chemie (1956.)

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FLUOROCYCLOHEXANES—II*

CIS- AND *TRANS*- 1H:3H- AND 1H:4H-DECAFLUOROCYCLOHEXANES†

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Abstract—An extension of the methods employed in the isolation of (*trans*) 1H/2H-decafluorocyclohexane,[1] (I) from the polyfluorocyclohexane mixture obtained by the vapour phase fluorination of benzene with cobaltic fluoride at about 150°, has afforded the four remaining members of the series of decafluorocyclohexanes [the *cis*- and *trans*- 1H:3H- and 1H:4H-isomers (1H:3H/-(IV), 1H/3H-(III), 1H:4H/-(VII), and 1H/4H-(VIII), respectively)] and also the *cis*-1H:2H-decafluorocyclohexane (II), obtained previously[1,2] by the lithium aluminium hydride reduction of 1:2-dichlorodecafluorocyclohexane. The structures of the 1H:3H- and 1H:4H-decafluorides have been established by dehydrofluorination studies. The six decafluorocyclohexanes have been related to two new nonafluorocyclohexanes[3] (IX and X) by further fluorination of the latter. 2H-Heptafluoroadipic acid has been obtained from 3H-nonafluorocyclohex-1-ene (V), one of the dehydrofluorination products of the 1H:3H-decafluorides.

By the passage of benzene in the vapour phase over cobaltic fluoride at about 150° a complex mixture of polyfluorocyclohexanes has been obtained.[1] This may be separated by fractional distillation controlled by analytical gas chromatography,[1,4] and pure fluorohydrocarbons isolated. The lowest boiling members, undecafluorocyclohexane[5,6] and 1H/2H-decafluorocyclohexane[1] (I) have been described already. The 1H:2H/-decafluoride (II) has also been made by a different method[2] and its structure proved.[1] In the present paper and the following one,[3] the characterisation of some higher-boiling components of the polyfluorocyclohexane mixture is described. In the first paper of this series[1] the results of a gas chromatographic analysis of this mixture were given in tabular form; the compounds to be described here gave peaks numbered 5, 6, 8 and 9.

Isolation of decafluorocyclohexanes

Further fractional distillation of the polyfluorocyclohexane mixture, obtained as before, gave, after removal of material boiling below 70°, a major fraction having b.p. 78° (peak 5). This had been investigated before[6,7,8] and was thought to be a pure compound, since it gave a single peak in analytical gas chromatography[8] using a dinonyl phthalate/kieselguhr packing (the only one available when the work was done).

* Part I was published in *J. Chem. Soc.* 2505 (1957).

† The nomenclature used is based on that suggested for hydroxycyclohexanes S. J. Angyal and C. G. Macdonald *J. Chem. Soc.* 686 (1952); D. H. Whiffen *Chem. & Ind. (Rev.)* 964 (1956).

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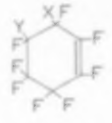
[7] D. E. M. Evans and J. C. Tatlow *J. Chem. Soc.* 3779 (1954).

[8] D. E. M. Evans and J. C. Tatlow *J. Chem. Soc.* 1184 (1955).

A 1H:3H-structure (III or IV) was then assigned to the compound, since dehydrofluorination[7,8] afforded octafluoro*cyclo*hexa-1:4- and -1:3-diene and 3H-(V) and 4*H*-nonafluoro*cyclo*hex-1-ene (VI). However, later investigations on gas chromatography[4] showed that, on other packings, notably silicone oil/silicone rubber, the fraction (5), b.p. 78°, was resolved into two components. For various reasons, at that time,

I 1Ha/2Ha (trans)
II 1Ha:2He/(cis)

III 1Ha/3He (trans)
IV 1Ha: 3Ha/(cis)



V X=H, Y=F
VI X=F, Y=H

VII 1Ha: 4He/(cis)
VIII 1Ha/4Ha (trans)

IX 1Ha: 4He/2Ha
X 1Ha/2Ha: 4Ha

preparative-scale gas chromatography tubes could not be operated with any of the packings which resolved the mixture. A partial separation of it was obtained by careful refractionation of the two intermediate mixtures having b.r. 71–78° and b.r. 79–85°, followed by separation of two subfractions obtained (b.r. 72–74° and 80–81° respectively) by preparative-scale gas chromatography over dinonyl phthalate/kieselguhr. This removed, respectively, the 1H/2H-decafluoride (I) b.p. 70°, and the decafluoride (6) b.p. 86° (see later), leaving two samples, one considerably enriched in the lower-boiling (5A) and the other in the higher-boiling (5B) component of the fraction of b.p. 78°. Preliminary investigations were carried out on these incompletely pure specimens. Later, an almost complete separation of the two components of fraction (5) (b.p. 78°) was achieved by a direct application of preparative-scale gas chromatography using a column packing of tricresyl phosphate/kieselguhr (1:3); the lower boiling isomer (5A) containing about 9 per cent of the higher one, the latter (5B) being obtained pure.

In another aspect of the present investigation (see later), two stereoisomeric nonafluoro*cyclo*hexanes were further fluorinated by cobaltic fluoride. *Inter alia*, compound (5A) free from (5B) was obtained from one nonafluoride, and compound (5B) free from (5A) from the other. Each was separated readily from the other products of fluorination by preparative-scale gas chromatography over dinonyl phthalate/kieselguhr, and was thus obtained completely pure. It was shown by infrared spectroscopy that the major component of the impure samples of compound (5A) was the same as this pure specimen, and likewise for compound (5B). Also, the original fraction (5), b.p. 78°, contained only the two components (5A) and (5B).

Fractional distillation of the polyfluoride mixture having boiling point greater than 79° gave a major fraction (peak 6[1]), b.p. 86°, which could not be resolved further by any available analytical gas chromatography packings and was pure.

Analytical gas chromatography[1] had shown that there were three compounds having boiling points near to 90°. One, a large fraction (peak 7), b.p. 92° is a nonafluoro-*cyclo*hexane and is described in a later paper.[3] The other two were small components (peaks 8 and 9) and they could not be separated by distillation, since all fractions boiling between 86° and 92° contained compounds 6, 7, 8 and 9. Accordingly, a fraction was taken with maximum concentrations of the new compounds, and separated by preparative-scale gas chromatography to give the two pure compounds (8) and (9). These had boiling points of 91° and 89° respectively, and it is of interest that in the series of three compounds (7, 8 and 9) the gas chromatographic retention times on a packing of dinonyl phthalate/kieselguhr are in the reverse order of boiling point.

*Dehydrofluorination studies on the decafluoro*cyclo*hexanes*

All of the compounds (5A, 5B, 6, 8 and 9) isolated as described above were shown by analysis to be decafluoro*cyclo*hexanes. Compound 8 (b.p. 91°) had a gas chromatographic retention time identical with that of the known 1H:2H/-decafluoro*cyclo*hexane[1,2] (II), and comparison of the infra-red spectra confirmed the identification.

The other four compounds were investigated by dehydrofluorination with aqueous potassium hydroxide. Compounds (5A) and (6) afforded three products, as shown by analytical gas chromatography, with retention times the same as those of octafluoro-*cyclo*hexa-1:4- and -1:3-diene and 4H-nonafluoro*cyclo*hex-1-ene (VI). No 3H-olefin (V) could be detected, however. Compounds (5B) and (9) gave four products, shown by analytical gas chromatography to be the two dienes mentioned above, and both the 3H- and the 4H-mono-olefins (V) and (VI). The identity of all of these olefins was proved conclusively by the separation of each of the four products into its components using preparative-scale gas chromatography, followed by comparisons of their infra-red spectra with those of known samples.[7,8] Also, the three olefins derived from compound (6) (b.p. 86°), the first to be investigated, were oxidised to give dibasic acids, difluoromalonic acid from the 1:4-diene, tetrafluorosuccinic from the 1:3-diene, and 3H-heptafluoroadipic from the 4H-olefin (VI).

The oxidation of the 3H-olefin (V) to give the derived dicarboxylic acid had been attended by experimental difficulty in the earlier work,[8] the acid and its derivatives being of doubtful purity. Accordingly, this process was re-examined. If the olefin was treated at about 70° with aqueous potassium permanganate containing sodium bicarbonate the primary product, 2H-heptafluoroadipic acid was obtained in good yield and it could be purified fairly readily. It was characterised as the free acid, dianilinium salt, and di-(S-benzylthiuronium) salt. The 2H-acid itself, as expected, was less stable than its 3H-isomer; fluoride ion was eliminated more readily on reaction with aqueous bases. However, it may be handled without unusual difficulty when pure and is fairly stable to heat. With aqueous permanganate at 100°, the 2H-acid was degraded, some tetrafluorosuccinic acid was formed as well as the hexafluoroglutaric acid reported earlier.[8] The 3H-olefin (V), with aqueous potassium permanganate at 100°, gave hexafluoroglutaric acid as reported before.[8] The samples of the derivatives of 2H-heptafluoroadipic acid obtained previously were essentially correct, but as suspected were contaminated with material from the breakdown of the olefin (V) and the 2H-acid itself arising because the oxidation was too vigorous.

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Structures of the decafluorocyclohexanes

Identification of the products obtained by dehydrofluorination of the decafluoro*cyclo*hexanes showed clearly that compounds (5A) and (6) which afforded no 3H-olefin (V) were 1H:4H-decafluorides (VII and VIII), whilst the other two (5B) and (9), which gave the 3H-olefin, were 1H:3H-compounds (III) and (IV). Preliminary indications of the stereochemistry of each compound were obtained by qualitative comparisons of the rates of dehydrofluorination. Assuming that the dehydrofluorination

Table 1. Comparative dehydrofluorinations of decafluoro*cyclo*hexanes

Decafluoro*cyclo*hexane under test			Dehydrofluorination reactions					
Fraction no.	Structure	b.p. (°C)	Conditions used	Relative peak sizes given by products				
				1:4-C_6F_8	1:3-C_6F_8	4H-C_6HF_9	3H-C_6HF_9	Starting material
6	1H:4H/-	86	A	*a*	*a*	*vw*	*a*	*vs*
5A	1H/4H-	78	A	*vw*	*vw*	*m*	*a*	*vs*
9	1H:3H/-	89	A	*vw*	*vw*	*w*	*w*	*vs*
5B	1H/3H-	78	A	*a*	*a*	*vw*	*vw*	*vs*
6	1H:4H/-	86	B	*m*	*m*	*vs*	*a*	*m*
5A	1H/4H-	78	B	*s*	*s*	*s*	*a*	*a*
9	1H:3H/-	89	B	*s*	*s*	*vs*	*s*	*a*
5B	1H/3H-	78	B	*s*	*m*	*s*	*s*	*m*

a = absent, *vw* = very weak, *w* = weak, *m* = medium, *s* = strong, *vs* = very strong.

mechanisms discussed in Part I of the series[1] apply here, then, for the preferred process to operate, the groups to be eliminated, hydrogen and fluorine, must both occupy axial positions. With 1H:3H- and 1H:4H-decafluorides there is always an axial fluorine substituent available on either side of a >CHF group in all possible conformations. If, as seems certain in the decafluoride series, the more stable conformations are those in which the small hydrogen substituents are carried where possible in axial positions, there should be two isomers with two axial hydrogen atoms and two with one axial and one equatorial hydrogen. The first two isomers should be dehydrofluorinated more readily than those with only one axial hydrogen, since both positions are available for attack by the base at the outset in the orientations required for the easiest elimination process to operate. In a series of comparative dehydrofluorination experiments (see Table) it was found that, under mild conditions, the 1H:4H-compound (6) (b.p. 86°) gave some of the 4H-olefin (VI) but no detectable amounts of either the octafluoro*cyclo*hexa-1:4- or -1:3-diene, whereas the stereoisomeric 1H:4H-compound (5A) gave readily detectable amounts of all these compounds. Likewise, with the 1H:3H-pair, the stereoisomer of b.p. 89° (compound 9) gave readily detectable amounts of the dienes and the mono-enes (V and VI), whereas the other compound (5B) gave mono-enes but no dienes. Correspondingly, when more vigorous reaction conditions were used, complete dehydrofluorination of all of the starting material occurred with compounds (5A) and (9), whereas appreciable amounts of the decafluoro*cyclo*hexanes remained with the other

pair, (5B) and (6). These results suggested strongly that compound (6), b.p. 86°, and the higher boiling component of the fraction of b.p. 78–79° (compound 5B) possess an equatorial hydrogen atom, i.e. they may be designated 1Ha:4He/- and 1Ha/3He-decafluoro*cyclo*hexane, respectively. The remaining two decafluorides possess diaxial hydrogen systems, i.e. the lower boiling component of the fraction b.p. 78–79° (compound 5A) is the 1Ha/4Ha-decafluoro*cyclo*hexane and compound (9), b.p. 89°, is the 1Ha:3Ha/-isomer.

These allocations of structure and those of the 1H:2H-compounds[1] could be tested by relating the decafluoro*cyclo*hexanes to two nonafluoro*cyclo*hexanes also obtained[3] from the polyfluoro*cyclo*hexane mixture. The nonafluorides were shown[3] by identification of dehydrofluorination products to be 1H:2H:4H-compounds; resolution of a derived 3H:4H-hexafluoroadipic acid in which the hydrogens retained the configuration of the original 1H:2H-system showed that both hydrogens of this were axial, i.e. *trans*, and rates of dehydrofluorination of the two isomers indicated that the lower-boiling one (b.p. 92°) was the 1Ha:4He/2Ha-compound (IX) and the other, b.p. 101°, was the 1Ha/2Ha:4Ha-stereoisomer (X).

These nonafluorides were fluorinated further by passage in the vapour phase over cobaltic fluoride in a small tubular static reactor. The nonafluoride (IX) gave five products, perfluoro*cyclo*hexane, undecafluoro*cyclo*hexane, and three decafluorides, the isomers 1Ha/2Ha- (I), b.p. 70°, 1Ha/3He-, (III), b.p. 78°, and 1Ha:4He/-(VII), b.p. 86°. Likewise, the nonafluoride (X) gave five products, perfluoro*cyclo*hexane, undecafluoro*cyclo*hexane, and three decafluorides, the isomers 1Ha/2Ha- (I), b.p. 70°, 1Ha:3Ha/- (IV), b.p. 89°, and 1Ha/4Ha- (VIII), b.p. 78°. Thus, the structures of the two series of compounds, deca- and nona-fluorides, arrived at independently, were related conclusively.

Infra-red measurements[9] of the C—H stretching frequencies of the six decafluorides also supported the stereochemical allocations made above. Final confirmation for the 1H:4H-decafluoro*cyclo*hexanes was obtained by measurements of the dipole moments of both isomers in benzene solutions. The observed dipole moments were: 1Ha/4Ha-decafluoro*cyclo*hexane (VIII) (b.p. 78°) 1·05 D (the accuracy of this determination was not high, but the true value could not exceed 1·5 D); 1Ha:4He/-decafluoro*cyclo*-hexane (VII) (b.p. 86°), 2·59D. Although these values, particularly the former, are only approximate, they demonstrate unequivocally the stereochemical configuration of each isomer, the *cis*-compound (VII), b.p. 86° possessing the larger dipole (2·59D) with which the calculated value (2·69D) is in good agreement. The lower boiling isomer (VIII) must therefore be the *trans*-compound.

All six decafluoro*cyclo*hexanes have thus been isolated and characterised conclusively. The structures, all suggested by dehydrofluorination reactions, are supported firmly by infra-red studies, and by dipole moments for the 1H:2H- and 1H:4H-pairs. Through the syntheses from the nonafluorides (IX and X), the 1H:3H-pair are related to all of these. The resolution of the acid derived from the nonafluorides (IX and X) is yet more proof of the structures of the 1H:2H-compounds. It must be noted that the fraction of b.p. 78° studied previously [6,7,8] was a mixture of the 1H/4H- and 1H/3H-isomers, which could not have been separated by the techniques then available. However, the products obtained by dehydrofluorination[7,8] were of course, pure, since the same olefins are derived from each. The decafluoro*cyclo*hexane mixture obtained[2]

[9] D. Steele and D. H. Whiffen *Tetrahedron* In press (1958).

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by lithium aluminium hydride reduction of the mixed dichlorodecafluoro*cyclo*hexane isomers formed[5] by fluorination of *o*-dichlorobenzene has been examined by gas chromatography. It was of interest to find that six components were present. They had retention times identical with those of the six decafluorides now characterised. The large predominance of the 1H:2H-decafluorides was confirmed and shows clearly that migration of chlorine occurs only to a limited degree.

From qualitative observations, it appears that the relative rates of dehydrofluorinations of the decafluorides follow the pattern to be expected. The 1H:2H/-isomer forms an olefin very readily, whilst the 1H/2H-compound is the slowest to react, for reasons discussed earlier.[1] The 1H/4H- and 1H:3H/-isomers also react easily, the former slightly more readily. This is understandable, since the two axial hydrogen atoms are separated on each side by two $>CF_2$ groups and so each should have slightly greater acidity than the hydrogens of the 1H:2H- and 1H:3H-series. Also, in the 1H/4H-compound the hydrogen atoms are far apart and on opposite sides of the *cyclo*hexane ring whilst in the 1H:3H/-compound they are close together. An interesting effect is the parallel between the proximity of hydrogen atoms in polyfluoro*cyclo*hexanes and their gas chromatography retention times and also their boiling points. Thus, in the decafluoride series, the two members with the hydrogens adjacent (1H:2H/- and 1H:3H/-) are retained longest and have the highest boiling points (91° and 89°, respectively). If the hydrogens are close together, intermolecular bindings appear to be stronger; the same effect is shown by nonafluoro*cyclo*hexanes.

EXPERIMENTAL

Isolation of the decafluorocyclohexanes

The mixture obtained from the fluorination of benzene,[1] after removal of compounds having boiling points <70°, was fractionally distilled using a heated vacuum-jacketed column (4 ft × $\frac{3}{4}$ in.) packed with Dixon gauze spirals ($\frac{1}{16}$ × $\frac{1}{16}$ in.). The fractionation was controlled by analytical gas chromatography (dinonyl phthalate/kieselguhr 1:2, temp. 80°, N_2 flow-rate 1·0 l/hr). Fractions were taken as follows:

Fraction A. This had b.p. 77–78°, and comprised 12–14 per cent of the mixture, giving a large flat region on the distillation curve. This fraction gave a single peak (no. 5 in Table 1[1]) on analytical gas chromatography, using dinonyl phthalate/kieselguhr packings even when large samples were injected (Found: C, 27·5; H, 1·0; F, 72·7. Calc. for $C_6H_2F_{10}$: C, 27·3; H, 0·8; F, 71·9%). However, with a column packing of silicone oil/silicone rubber[5] (1:10) (temp. 78°, N_2 flow-rate 1·0 l/hr.) the fraction was resolved into two components of approximately equal proportions; a column packing of tricresyl phosphate/kieselguhr (1:3) gave a less sharp resolution of the two components. The infra-red spectrum of the mixture was measured between 3000 and 650 cm^{-1} in the vapour state and displayed absorptions attributable to the 1H/4H- and 1H/3H-decafluoro*cyclo*hexanes prepared separately by cobaltic fluoride fluorination of two of the 1H:2H:4H-nonafluoro*cyclo*hexanes (see later). No other compounds were present.

An almost complete separation was effected, using preparative-scale gas chromatography in a tube 20 ft × 3·5 cm i.d. packed with tricresyl phosphate/kieselguhr 1:3 (temp 40°, N_2 flow-rate 9 l/hr). The two components were identified by infra-red spectroscopy as 1H/4H-decafluoro*cyclo*hexane containing about 9 per cent of the 1H/3H-isomer, and as the 1H/3H-compound, free of the other isomer.

Fraction B. This had b.p. 86·0–86·5°, and was 3–5 per cent of the mixture, giving a considerable flat part on the distillation curve. It gave a single peak (no. 6 in Table 1[1]) on analytical gas chromatography, even when large samples were injected and various packings used, viz. dinonyl phthalate/kieselguhr, tricresyl phosphate/kieselguhr, silicone oil/silicone rubber. It was 1H:4H/-*decafluoro*cyclo*hexane*, b.p. 86°, m.p. 40–41° (Found: C, 27·0; H, 0·8%).

Fractions with b.r. 70–77° and 78–86° were mixtures and no new components were detected by gas chromatography.

Fraction C. Material of b.r. 87–92° was shown by analytical gas chromatography to contain 4 compounds. These were the 1H:4H/-decafluoride (b.p. 86°) (peak 6[1]), 1H:4H/2H-nonafluoro*cyclo*hexane[3] (b.p. 92°) (peak 7[1]) and two new components (peaks 8 and 9[1]). Separation by distillation was impossible, so the fraction with the maximum concentration of the new compounds (Fraction C, b.r. 91·2–91·7°) was separated by preparative-scale gas chromatography (tube 16 ft × 3 cm packed with dinonyl phthalate/kieselguhr 1:2, temp. 100°, N_2 flow-rate 10 l./hr). The first and second compounds to be obtained in this way were the 1H:4H/-decafluoro*cyclo* hexane (b.p. 86°) and the 1H:4H/2H-nonafluoro*cyclo*hexane[3] (b.p. 92°). The third compound (b.p. 91°) was 1H:2H/-decafluoro*cyclo*hexane (peak 8). The gas chromatography retention times and infra-red absorption spectrum over the range 1800–700 cm^{-1}, were identical with those of the *cis*-isomer obtained by lithium aluminium hydride reduction of 1:2-dichlorodecafluoro*cyclo*hexane in ether.[1,2]

The fourth and last compound (peak 9) (b.p. 89°, m.p. 35–40°) (Found: C, 27·3; H, 0·8; F, 71·4%) was 1H:3H/-*decafluoro*cyclo*hexane*. The overall yield of the above two decafluorides was 0·5–1 per cent of the original polyfluoride mixture.

*Fluorination of nonafluoro*cyclo*hexanes*

Fluorination apparatus. This consisted of a horizontal copper tube (17 in. long; 2 in. i.d.; $\frac{1}{8}$ in. wall thickness) completely packed with a mixture of cobaltic fluoride (300 g) and $\frac{1}{2}$ in. nickel gauze cylinders (500 cc). The end plates were made from Yorkshire-type unions into which were brazed $\frac{1}{4}$ in. o.d. copper pipes. The tube was heated by three sectional heaters of the improved design described before.[1] The compounds, introduced at a steady rate as liquids from an electrically heated microburette, were vapourised, the vapours passed over the fluorinating agent, and the products were collected in a trap cooled by solid CO_2. When the addition was complete the apparatus was swept out for ca. 30 min with a slow stream of nitrogen, and the trap was then warmed to room temperature and the contents poured into water. After each fluorination the cobaltic fluoride in the reaction vessel was regenerated by passage at about 150° of fluorine (ca. 25 g) during $1\frac{1}{2}$ hr. After being swept through with nitrogen, the reactor was again ready for use.

Fluorination of 1H/2H:4H-*nonafluoro*cyclo*hexane.* The nonafluoro*cyclo*hexane,[3] (16 g, b.p. 101°) was passed during 1 hr over cobaltic fluoride at about 150° in the vessel described above. Gas chromatographic analysis of the waxy solid product (17 g) (after the addition of a little ether to a small sample) revealed the presence of six components. The mixture (4·29 g) was separated by preparative-scale gas chromatography (column 16 ft × 3 cm, packed with dinonyl phthalate/kieselguhr 1:2, temp. 98°, N_2 flow-rate 9 l/hr) to give a trace of perfluoro*cyclo*hexane, b.p. 52°; undecafluoro*cyclo*hexane, b.p. 63° (0·32 g); 1H/2H-decafluoro*cyclo*hexane, b.p. 70° (0·18 g),

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1H/4H-*decafluoro*cyclo*hexane*, b.p. 78°, (1·14 g) (Found: C, 27·2; H, 0·8%); 1H:3H/-decafluoro*cyclo*hexane, b.p. 89° (0·34 g); and unchanged 1H/2H:4H-nonafluoro*cyclo*hexane, b.p. 101° (1·23 g). These compounds had infra-red spectra identical with those of the analogous samples described above. The gas chromatography retention times were also the same.

Fluorination of 1H:4H/2H-*nonafluoro*cyclo*hexane*. The nonafluoro*cyclo*hexane (16 g, b.p. 93°) was passed during 40 min over cobaltic fluoride at about 150° to give a waxy solid product (15 g). A portion (4·4 g) of this was dissolved in ether and separated by preparative-scale gas chromatography (column 16 ft × 3 cm, dinonyl phthalate/kieselguhr 1 : 2, temp. 103°, N_2 flow-rate 9·0 l/hr) to give perfluoro*cyclo*hexane, b.p. 52° (0·01 g); undecafluoro*cyclo*hexane, b.p. 63° (0·54 g); 1H/2H-decafluoro-*cyclo*hexane, b.p. 70° (0·09 g); 1H/3H-*decafluoro*cyclo*hexane*, b.p. 78° (0·55 g) (Found: C, 27·5; H, 1·0%); 1H:4H/-decafluoro*cyclo*hexane, b.p. 86° (0·50 g); and unchanged 1H:4H/2H-nonafluoro*cyclo*hexane, b.p. 93° (1·35 g). The compounds of this mixture were identified by their chromatographic retention times and by measurement of their infra-red absorption spectra, which were identical in all cases with those of analogous samples.

Dehydrofluorination of 1H:4H/-*decafluoro*cyclo*hexane*. The decafluoro*cyclo*hexane (1·5 g, b.p. 86°) was boiled for 4 hr with potassium hydroxide (1·5 g) in water (7·5 cc). The organic phase was separated, washed and dried ($MgSO_4$). Analytical vapour phase chromatographic examination of the product (dinonyl phthalate/kieselguhr 1 : 2, temp. 84°, N_2 flow-rate 1·2 l/hr) revealed three peaks at the same retention times as those from authentic specimens of [7,8] respectively, octafluoro*cyclo*hexa-1:4-, and -1:3-diene and 4H-nonafluoro*cyclo*hexene. No 3H-nonafluoro*cyclo*hexene[8] could be detected, even when large samples were injected.

In a preparative-scale reaction, the 1H:4H/-compound (10·00 g) was refluxed with potassium hydroxide (10 g) in water (50 cc) for 4½ hr. The organic layer (7·97 g) was separated, dried ($MgSO_4$) and fractionated in the preparative-scale gas chromatographic column[4] (16 ft × 3 cm packed with dinonyl phthalate/kieselguhr 1 : 2) to give octafluoro*cyclo*hexa-1:4-diene (1·34 g), octafluoro*cyclo*hexa-1:3-diene (0·50 g) and 4H-nonafluoro*cyclo*hexene (5·82 g). These had infra-red spectra in the vapour phase over the range 1800–700 cm^{-1} identical with those of specimens obtained previously.[7,8]

Oxidations of these olefins were carried out as described before,[5,7,8] and confirmed the earlier results. The 1:4-diene afforded difluoromalonic acid, the 1:3-diene gave tetrafluorosuccinic acid, and the 4H-olefin gave 3H-heptafluoroadipic acid. All were identified as their dianilinium and di-(*S*-benzylthiuronium) salts, which were obtained in good yields and with the correct elemental analyses.

Dehydrofluorination of 1H/4H-*decafluoro*cyclo*hexane*. The decafluoro*cyclo*hexane (4·5 g, b.p. 78°, obtained from the fluorination of 1H/2H : 4H-nonafluoro*cyclo*hexane) was kept at room temperature for 15 hr in contact with a solution of potassium hydroxide (1 g) in water (9 cc) with intermittent agitation. The organic layer was then separated and analysed by gas chromatography (dinonyl phthalate/kieselguhr 1 : 2, temp. 99°, N_2 flow-rate 1·15 l/hr); this revealed the presence of three products and the starting material, the retention times being identical with those of authentic samples of octafluoro*cyclo*hexa-1:4-diene, octafluoro*cyclo*hexa-1:3-diene, 4H-nonafluoro*cyclo*hexene and the unchanged decafluoro*cyclo*hexane. The mixture (3·05 g) was separated by preparative-scale gas chromatography (column 16 ft × 3 cm,

dinonyl phthalate/kieselguhr 1 : 2, temp. 87°, N_2 flow-rate 10 l/hr) into octafluoro*cyclo*hexa-1:4-diene (0·12 g), octafluoro*cyclo*hexa-1:3-diene (0·01 g), 4H-nonafluoro*cyclo*hexene (2·03 g) and the *trans*-1H:4H-decafluoro*cyclo*hexane (0·30 g). No 3H-olefin was found. The 4H-nonafluoro*cyclo*hexene possessed an infra-red absorption spectrum over the range 1800–650 cm^{-1}, identical with that of authentic specimens.

When the 1H/4H-decafluoride (0·5 g) was refluxed for 2 hr with potassium hydroxide (0·5 g) in water (3·0 cc) the product contained only the 1:3- and 1:4-dienes, no starting material or 4H-olefin being present.

Dehydrofluorination of 1H/3H-*decafluoro*cyclo*hexane*. The decafluoro*cyclo*hexane (3·5 g, b.p. 78°, obtained by fluorination of the 1H:4H/2H-nonafluoro*cyclo*hexane), was refluxed with potassium hydroxide (0·8 g) in water (8 cc) for 8 hr. The organic layer was separated and analysed by gas chromatography (dinonyl phthalate/kieselguhr 1 : 2, temp. 92°, N_2 flow-rate 1·5 l/hr); this revealed the presence of four components (in addition to unchanged starting material) with retention times identical with those of authentic specimens of the octafluoro*cyclo*hexa-1:4- and -1:3-dienes and the 4H- and 3H-nonafluoro*cyclo*hexenes, respectively. The mixture (2·46 g) so obtained was separated by preparative scale gas chromatography (column 16 ft × 3 cm, dinonyl phthalate/kieselguhr 1 : 2, temp. 100°, N_2 flow-rate 8·9 l/hr) into octafluoro*cyclo*hexa-1:4-diene (ca. 0·01 g), octafluoro*cyclo*hexa-1:3-diene (ca. 0·01 g), 4H-nonafluoro*cyclo*hexene (1·09 g), 3H-nonafluoro*cyclo*hexene (0·99 g) and unchanged 1H/3H-decafluoro*cyclo*hexane (0·02 g); these fractions displayed infra-red absorption spectra identical with those of authentic specimens of these compounds over the range 1800–700 cm^{-1}.

Dehydrofluorination of 1H:3H/-*decafluoro*cyclo*hexane*. The decafluoro*cyclo*hexane (3·77 g, b.p. 89°) was refluxed for 3 hr with potassium hydroxide (4·0 g) in water (20 cc). The organic phase was separated, washed and dried ($MgSO_4$). Analytical gas chromatographic examination of the product (dinonyl phthalate/kieselguhr 1 : 2, temp. 86°, N_2 flow-rate 1·2 l/hr) revealed four peaks with the same retention times as those exhibited by authentic specimens of, respectively, octafluoro*cyclo*hexa-1:4- and -1:3-dienes, and 4H- and 3H-nonafluoro*cyclo*hexene. The mixed olefins (1·64 g) were separated in a preparative-scale gas chromatography column (16 ft × 3 cm, dinonyl phthalate/kieselguhr 1 : 2, temp. 88°, N_2 flow-rate 10 l/hr) to give octafluoro*cyclo*hexa-1:4-diene (0·41 g), octafluoro*cyclo*hexa-1:3-diene (0·26 g), 4H-nonafluoro*cyclo*hexene (0·41 g) and 3H-nonafluoro*cyclo*hexene (0·30 g). Each of the above components was identified by measurement of the infra-red absorption spectrum between 1800 and 700 cm^{-1} and comparison of them with those of authentic specimens.

Oxidation of 3H-*nonafluoro*cyclo*hex*-1-*ene*. The olefin (3·2 g), potassium permanganate (12·0 g), sodium bicarbonate (4·3 g) and water (70 cc) were shaken together for 18 hr at 65–70° in a rocking autoclave. After isolation as usual,[5] there was obtained a crude acidic product (2·3 g) which was distilled (130–140°/0·2 mm) to give a white hygroscopic solid (recovery 60 per cent). After being dried this 2H-*heptafluoroadipic acid* had m.p. 116–117° (Found: C, 26·9; H, 1·4%; equiv. 133. $C_6H_3O_4F_7$ requires C, 26·5; H, 1·1%; equiv. 136). Reaction of the acid (0·2 g) with aniline in ether gave a solid which was recrystallised from chloroform–acetone to give a *dianilinium salt* (0·2 g), m.p. 169–170° (Found: C, 47·2; H, 3·7. $C_{18}H_{17}O_4N_2F_7$ requires C, 47·2; H, 3·7%). Treatment of the dianilium salt (0·038 g) with

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S-benzylthiuronium chloride in water at pH 4 gave the *di*-(S-*benzylthiuronium*) *salt* (0·029 g), m.p. 232–233° (Found: C, 43·6; H, 3·7. $C_{22}H_{23}O_4N_4S_2F_7$ requires C, 43·7; H, 3·8%).

Preparation of a pure amide by esterification of the acid and treatment with ammonia was difficult because of elimination of fluoride ion during the ammonolysis.

With aqueous potassium hydroxide (1 N or 2 N) considerably more fluoride ion was lost from the 2H- than from 3H-heptafluoroadipic acid.

Comparative dehydrofluorinations of the 1H:4H- *and the* 1H:3H-*decafluorocyclohexanes*. The four compounds under test (0·5 g) were each covered with a solution of potassium hydroxide (0·8 g) in water (3 cc) and the mixtures kept at 50° for 1¼ hr with intermittent shaking (reaction conditions A). Test samples of the organic layers were then analysed qualitatively by gas chromatography (dinonyl phthalate/kieselguhr 1 : 2, temp. 96°, N_2 flow-rate 1·5 l/hr) under standard conditions. The reaction mixtures were then refluxed for a further 4 hr (reaction conditions B) and the organic layers were again subjected to gas chromatographic analysis under standard conditions. The results of the gas chromatographic analysis are given in Table 1.

Dipole moment measurements on 1H:4H-*decafluorocyclohexanes*. The apparatus and method employed were the same as before.[1] Measurements on the 1H:4H/-isomer (b.p. 86°), using solutions in benzene with concentrations up to 14 per cent by weight, gave an orientation polarisation of 139·4 ± 7·4 cc/mole, which is equivalent to a dipole moment of 2·59 ± 0·07 D. Only limited amounts of absolutely pure 1H/4H-isomer (b.p. 78°) were available, so that the solutions used had maximum concentrations of only ca. 4 per cent by weight. The measured orientation polarisation was 22·9 cc/mole, giving a dipole moment of 1·05 D, but the estimated limits of error in the former are ±22·2 cc/mole, so that the dipole moment could be in the range 0·2–1·5 D. However, it must be emphasised that the purpose of this experiment was to confirm the stereochemical structures of the two isomers. This has been done unequivocally, though the accuracy of the actual results obtained for the dipole moments, particularly for the 1H/4H-isomer, is not high.

Infra-red spectra. Some aspects of these are discussed in the following papers.[9,10] The complete spectra of the compounds described are included in the Documentation of Molecular Spectra issued by Butterworths.

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[10] J. Burdon and D. H. Whiffen *Tetrahedron* To be submitted shortly.

Tetrahedron, 1958, Vol. 2, pp. 193–202. Pergamon Press Ltd., London

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FLUOROCYCLOHEXANES—III*

1H:4H/2H- AND 1H/2H:4H-NONAFLUOROCYCLOHEXANE† AND DERIVED COMPOUNDS

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Abstract—Two nonafluorocyclohexanes of b.p. 92° and 101°, made by fluorination of benzene,[1] have each been dehydrofluorinated to give the same six unsaturated products. These were identified by oxidation and other studies as 3H:4H- and 4H:5H-octafluorocyclohexene, 1H-1:4-, 1H-1:3-, and 2H-1:3-heptafluorocyclohexadiene, and hexafluorobenzene,[2] thus indicating a 1H:2H:4H-structure for the saturated precursors. The stereochemistry of the adjacent >CHF groups was established by resolution, via the brucine salt, of the 3H:4H-hexafluoroadipic acid obtained by oxidation of the 4H:5H-mono-olefin, showing that the hydrogens were *trans*. The complete stereochemistry of the nonafluorides was suggested by the dehydrofluorinations and confirmed by further fluorination[3] to give known decafluorocyclohexanes. Treatment of 4H/5H-octafluorocyclohexene with lithium aluminium hydride in diethyl ether gave 1H,4H/5H-heptafluorocyclohexene, a precursor of pentafluorobenzene.[4]

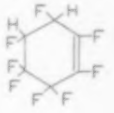
ISOLATION AND DEHYDROFLUORINATION OF THE NONAFLUOROCYCLOHEXANES

FROM the polyfluorocyclohexane mixture[1] made from benzene, two new fluorohydrocarbons (b.p. 92°, m.p. 45°, and b.p. 101°, m.p. 12–14°) have been isolated by fractional distillation controlled by analytical gas chromatography.[5] Each was a nonafluorocyclohexane, and when dehydrofluorinated exhaustively with aqueous potassium

I 1Ha : 4He/2Ha
II 1Ha/2Ha : 4Ha

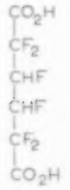
III X=F, Y=H
VII X=H, Y=F

IV X=H, Y=F
V X=F, Y=H



VI 3H/4H

VIII X=F
X X=H
both 4H/5H



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* Part II, preceding paper.

† The nomenclature used for these cyclohexane derivatives follows that of the inositols (see S. J. Angyal and C. G. Macdonald *J. Chem. Soc.* 686 (1952); D. H. Whiffen *Chem. & Ind. (Rev.)* 964 (1956).

[1] R. P. Smith and J. C. Tatlow *J. Chem. Soc.* 2505 (1957).
[2] J. A. Godsell, M. Stacey, and J. C. Tatlow *Nature, Lond.* **178**, 199 (1956).
[3] D. E. M. Evans, J. A. Godsell, R. Stephens, J. C. Tatlow and E. H. Wiseman *Tetrahedron* **2**, 183 (1958).
[4] R. Stephens and J. C. Tatlow *Chem. & Ind. (Rev.)* 821 (1957).
[5] D. E. M. Evans and J. C. Tatlow *Vapour Phase Chromatography* (Edited by D. H. Desty) p. 256. Butterworths, London (1956).

hydroxide, a relatively difficult reaction in both cases, each gave a mixture (boiling range 66–90°), which was shown by analytical gas chromatography to contain six compounds. Preparative-scale gas chromatography[5] effected the separation of these two mixtures into their components, and it was demonstrated by infra-red spectroscopy,[6,7] and by the identity of the gas chromatographic retention times, that the six products from one nonafluoride were individually the same as those from the other.

CHARACTERISATION OF THE DEHYDROFLUORINATION PRODUCTS

The six compounds formed in the dehydrofluorinations were characterised by oxidative degradation and other studies. The first substance isolated (b.p. 66–67°) analysed as a heptafluoro*cyclo*hexadiene, and was oxidised by aqueous potassium permanganate to give difluoromalonic acid. It showed two bands in the infra-red[7] corresponding to a —CF=CF— and a —CF=CH— double bond, but no strong selective absorption in the ultra-violet (such absorption would have been given by a conjugated diene). These facts showed clearly that the compound was 1H-heptafluoro*cyclo*hexa-1:4-diene (III).

The second and third fractions obtained (b.p. 72° and 76°, respectively) were also heptafluoro-dienes. Each was oxidised to tetrafluorosuccinic acid, and each gave a tetrachloro-addition product with chlorine. Spectroscopically, each gave a strong selective absorption band in the ultra-violet, showing the presence of a conjugated system, and two C=C bands in the infra-red.[7] Thus, these two compounds were 1H- and 2H-heptafluoro*cyclo*hexa-1:3-diene (IV and V), but as yet it has not been possible to decide which compound possesses which structure. Attempts to saturate selectively one of the double bonds of the conjugated system of each compound by reaction with cobaltic fluoride under very mild conditions, which might have given a different range of nonafluoro*cyclo*hexenes in the two cases, were not successful. It is of interest that these conjugated dienes exhibited similar instability when exposed to the atmosphere to that shown [8] by perfluoro*cyclo*hexa-1:3-diene.

The fourth product isolated from the original dehydrofluorination had b.p. 80° and was hexafluorobenzene; its characterisation has been described already.[2]

The fifth compound had b.p. 85° and was an octafluoro*cyclo*hexene. Addition of chlorine gave a dichloro-octafluoro*cyclo*hexane, and the presence of a —CF=CF— group was indicated by infra-red analysis.[7] Oxidation afforded a hexafluoroadipic acid, proving that no hydrogen was carried directly on the double bond. When the acid was treated with alkaline potassium permanganate, tetrafluorosuccinic acid was produced. The hexafluoroadipic acid was very susceptible to attack by bases, attempts to prepare an anilinium salt and an amide failing. This behaviour is typical[3,9] of acids with α-carbons carrying hydrogen and β-carbons carrying fluorine substitutents. All this evidence shows that the acid was 2H:3H-hexafluoroadipic acid, and, from the work on the stereochemistry of the —CHF—CHF— system in all these compounds (see later), it can be given the DL-*threo*-configuration. The original olefin was thus 3H:4H-octafluoro*cyclo*hex-1-ene (VI). Confirmation of this structure was obtained by dehydrofluorination, which afforded 3 products, identified by gas

[6] D. Steele and D. H. Whiffen. In press.
[7] J. Burdon and D. H. Whiffen. *Tetrahedron* (to be submitted shortly).
[8] D. E. M. Evans and J. C. Tatlow *J. Chem. Soc.* 3779 (1954).
[9] M. W. Buxton, M. Stacey and J. C. Tatlow *J. Chem. Soc.* 366 (1954).

chromatography and infra-red spectroscopy as the two conjugated dienes (IV and V) and hexafluorobenzene. The last compound presumably must have been formed by a 1:4-elimination process from 3H-heptafluoro*cyclo*hexa-1:4-diene (VII), though this intermediate was not found in the product formed under the reaction conditions employed. Neither hexafluorobenzene nor the 4H:5H-olefin (VIII), which gives it by a 1:2-elimination, could be detected in the sample of the starting material (VI) used.

The sixth product (b.p. 90°) of the reaction of the nonafluorides (I and II) with alkali was another octafluoro*cyclo*hexene which gave a dichloro-addition product, and had an infra-red spectrum[7] suggesting the presence of a CF=CF group. This was confirmed by the production of a new hexafluoroadipic acid upon oxidation. Degradation of this C_6-acid with alkaline permanganate afforded difluoromalonic acid. This established the structure of the former as 3H:4H-hexafluoroadipic acid (IX), and thence of the original olefin as 4H:5H-octafluoro*cyclo*hex-1-ene (VIII). The latter structure was confirmed by dehydrofluorination, which proceeded only slowly but afforded two products, the 1H-1:4-diene (III) and hexafluorobenzene.

STRUCTURES OF THE NONAFLUORO*CYCLO*HEXANES

The dehydrofluorination products obtained from the nonafluoro*cyclo*hexanes (I) and (II) showed clearly that the latter must be 1H:2H:4H-compounds. By orthodox elimination processes, 1H:2H:3H-nonafluorides could not give the 4H:5H-olefin (VIII) or the unconjugated diene (III), whilst 1H:3H:5H-nonafluorides could give only hexafluorobenzene of the products found. The pattern of unsaturated derivatives obtained also indicated that, with both nonafluorides, the isolated hydrogen on position 4 was the initial point of attack. By analogy with the results obtained earlier[1] for the 1H:2H-decafluoro*cyclo*hexanes, this suggested that the hydrogens on carbon atoms 1 and 2 were *trans*, and hence that, being smaller than fluorine, they occupied *axial* positions. An unequivocal method for establishing the stereochemistry of this part of the molecule was available, however. The configuration of the asymmetric carbon atoms (3 and 4) of the 3H:4H-hexafluoroadipic acid (IX), obtained by oxidation of the olefin (VIII), was clearly the same as that of carbon atoms 1 and 2 of both of the parent nonafluoro*cyclo*hexanes. If this arrangement was *trans*, i.e. if each of the hydrogens was *axial*, the hexafluoroadipic acid must be a DL-mixture which would be resolvable. If one hydrogen was *axial* and one *equatorial*, the derived acid would be an optically inactive *meso*-form. By the classical method of resolution, fractional crystallisation of the brucine salts, the 3H:4H-hexafluoroadipic acid (IX) was resolved successfully into its *dextro*- and *laevo*-enantiomorphs. This proved conclusively that both of the nonafluoro*cyclo*hexanes (I and II) were *trans* (1Ha/2Ha)-isomers. Obviously, the mono-olefins (VI and VIII) also had the *trans*-structure, and were, respectively, 3H/4H-, and 4H/5H-octafluoro*cyclo*hex-1-ene. A qualitative comparison of the rates of dehydrofluorination of the nonafluorides (I and II) indicated that the isomer (II) (b.p. 101°) reacted more readily under mild conditions to give the two mono-olefins (VI and VIII) than did the isomer (I). It was assumed therefore that the former (II) had a 4Ha-structure, and the latter (I) a 4He-structure.

Confirmation of these configurations was provided by further fluorination of the nonafluorides (I and II) using cobaltic fluoride. The experimental details of these reactions are described in the previous paper[3]. The isomer (I) gave 3 decafluoro*cyclo*-hexanes which have been shown by independent studies[3] to possess the 1Ha/2Ha

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(b.p. 70°), the 1Ha/3He (b.p. 78°) and the 1Ha:4He/ (b.p. 86°) structures. The isomer (II) likewise gave the known[8] 1Ha/2Ha, 1Ha:3Ha/ (b.p. 89°), and 1Ha/4Ha (b.p. 78°) decafluorides. Hence, the two parent compounds investigated in this paper are 1Ha:4He/2Ha- (I) and 1Ha/2Ha:4Ha-nonafluoro*cyclo*hexane (II). The two independent studies of the decafluoride and the nonafluoride series have thus been related completely, the structural assignments in each being supported by those in the other. Further evidence confirming the stereochemical allocations has also been obtained from the infra-red studies.[6]

The isolation of the mono-olefin (VIII) enabled a synthesis to be effected of the then unkown aromatic compound pentafluorobenzene. Earlier work[10] in this department has shown that ethereal lithium aluminium hydride reacts readily with fluoroolefins, with progressive replacement of vinylic fluorines by hydrogen, probably by an addition-elimination mechanism. 4H/5H-Octafluoro*cyclo*hexene (VIII) reacted with the metal hydride in this way to give 1H, 4H/5H-heptafluoro*cyclo*hex-1-ene (X), together with two new hexafluoro*cyclo*hexenes that were not investigated. The structure of the heptafluoride (X) was confirmed by its infra-red spectrum[7] (a band at 1710 cm^{-1} indicated a CF═CH group) and by oxidation to give the same hexafluoroadipic acid (IX) as had been formed from the parent octafluoride (VIII). Dehydrofluorination of the heptafluoride (X) afforded the desired pentafluorobenzene. However; an easier synthesis of this new fluoro-aromatic compound had by then been developed,[4] starting from a major component of the polyfluoro*cyclo*hexane mixture, a 1H:2H:4H:5H-octafluoro*cyclo*hexane.

Interesting new fields of study are opened up by these syntheses of aromatic polyfluoro-compounds from members of the fluoro*cyclo*hexane series.

EXPERIMENTAL

1H:4H/2H- *and* 1H/2H:4H-*nonafluoro*cyclo*hexane*

Fractional distillation controlled by analytical gas chromatography[5] of the partly fluorinated *cyclo*hexane mixture[1,3] having b.p. > 91·7° gave[2] 1H:4H/2H- (b.p. 92·0–92·5°, m.p. 44–46°), a mixed intermediate fraction, and 1H/2H:4H-*nonafluoro*cyclo*hexane*, b.p. 101°, m.p. 12–14°, n_D^{14} 1·3194 (Found: C, 29·4; H, 1·2. Calc. for $C_6H_3F_9$: C, 29·3; H, 1·2%). These nonafluorides were obtained in yields of, respectively, ca. 10 per cent and ca. 5 per cent of the original polyfluoride mixture. These yields may be increased by using lower fluorination temperatures.

The 1H:4H/2H-isomer gave peak no. 7 in the table of gas chromatography results given earlier.[1] The other isomer was peak no. 12, but under the conditions used resolution is inferior for the compounds of long retention times.

Dehydrofluorination of 1H:4H/2H-*nonafluoro*cyclo*hexane*

The polyfluoride (11·0 g, b.p. 92°), potassium hydroxide (10·0 g) and water (10 cc) were heated together under reflux for 6 hr (two condensers in series were used, one cooled by water and one by solid carbon dioxide). The organic phase (9·0 g) was separated, washed with water, and dried ($MgSO_4$). Analytical gas chromatography (dinonyl phthalate/kieselguhr 1 : 2, temp. 82°, N_2 flow rate 1·6 l/hr) showed 6 peaks with retention times (in minutes) of 9·1 (*w*), 11·3 (*m*), 15·7 (*w*), 25·5 (*w*), 28·5 (*vs*), and 33·5 (*s*), respectively. Separation of the mixture in the preparative-scale gas

[10] D. E. M. Evans and J. C. Tatlow Unpublished results.

chromatography column[5] (16 ft long × 3 cm dia., dinonyl phthalate/kieselguhr 1 : 2, temp. 80°, N_2 flow rate 10 l/hr), followed by distillation of each fraction *in vacuo*, afforded respectively: (i) 1H-*heptafluoro*cyclo*hexa*-1:4-*diene* (0·18 g), b.p. 66·5–67·0°, n_D^{18} 1·3275 (Found: C, 35·1; H, 0·6. Calc. for C_6HF_7: C, 35·0; H, 0·5%); (ii) *heptafluoro*cyclo*hexa*-1:3-*diene* (1·37 g), b.p. 71·5–72·5°, n_D^{18} 1·3400 (Found: C, 34·7; H, 0·4%); (iii) *heptafluoro*cyclo*hexa*-1:3-*diene* (0·51 g), b.p. 76°, n_D^{18} 1·3383 (Found: C, 35·1; H, 0·7%); (iv) hexafluorobenzene (0·46 g), b.p. 80°, n_D^{18} 1·3746 (Found: C, 38·6; F, 62·0. Calc. for C_6F_6: C, 38·7; F, 61·3%); (v) 3H/4H-*octafluoro*cyclo*hex*-1-*ene* (3·75 g), b.p. 85°, n_D^{18} 1·3277 (Found: C, 31·6; H, 0·9; F, 66·9. Calc. for $C_6H_2F_8$: C, 31·9; H, 0·9; F, 67·2%); and (vi) 4H/5H-*octafluoro*cyclo*hex*-1-*ene* (2·51 g), b.p. 90°, n_D^{18} 1·3283 (Found: C, 32·2; H, 1·2%).

The relative proportions of the products were varied by alteration of the reaction conditions, more drastic treatment increased the amounts of products (i)–(iv) at the expense of (v) and (vi), particularly of (v), which was dehydrofluorinated more readily than (vi).

The conjugated dienes (ii) and (iii) were unstable, and after a few days samples became turbid and hydrogen fluoride was present (cf. octafluoro*cyclo*hexa-1:3-diene[8]). This decomposition was retarded by storage in well-stoppered vessels at 0°.

In the early stages of the work[5] it was thought that nine products were formed in this dehydrofluorination. However, three of these gave only very small peaks with low retention times in gas chromatography. They were identified later as perfluoro*cyclo*hexa-1:3- and -1:4-diene, and 1H-nonafluoro*cyclo*hexene, and arose[3] from traces of 1H:3H/- (b.p. 89°), and 1H:2H/- decafluoro*cyclo*hexane (b.p. 91°), respectively, in the nonafluoride samples. These impurities are removed by careful fractional distillation as described above.

Characterisation of 1H-*heptafluoro*cyclo*hexa*-1:4-*diene*

(a) *Oxidation*. The diene (1·12 g), potassium permanganate (10 g), and water (50 cc) were shaken in an autoclave at 20° for 14 hr and the temperature was then raised to 100° for 4 hr. Isolation as usual [8,11] gave dianilinium difluoromalonate (42 per cent), m.p. 161–162° (from acetone–chloroform) (Found: C, 55·0; H, 4·8%; equiv., 164. Calc. for $C_{15}H_{16}O_4N_2F_2$: C, 55·2; H, 4·9%; equiv., 163) and di-(*S*-benzylthiuronium) difluoromalonate, m.p. 184–185° (Found: C, 48·2; H, 4·8. Calc. for $C_{19}H_{22}O_4N_4S_2F_2$: C, 48·3; H, 4·7%). Cited[8] melting points were 160–161° and 180–182°, respectively.

(b) *Spectroscopy*. The diene showed two bands in the infra-red at 1723 and 1770 cm^{-1}. No selective absorption was shown in the ultra-violet over the range 2400–3000 Å.

*Characterisation of the heptafluoro*cyclo*hexa*-1:3-*diene of b.p.* 72°

(a) *Oxidation*. Treatment as usual at 100° for 17 hr with aqueous permanganate afforded, by the standard isolation process,[8] dianilinium tetrafluorosuccinate (20 per cent), m.p. 224–225° (Found: C, 51·2; H, 4·4%; equiv., 187. Calc. for $C_{16}H_{16}O_4N_2F_4$: C, 51·1; H, 4·3%; equiv., 188). The di-(*S*-benzylthiuronium) salt had m.p. 189–190° (Found: C, 45·8; H, 4·4. Calc. for $C_{20}H_{22}O_4N_4S_2F_4$: C, 46·0; H, 4·2%). Cited[8] melting points were 224–225°, and 189–190°, respectively.

[11] J. C. Tatlow and R. E. Worthington *J. Chem. Soc.* 1251 (1952).

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(b) *Addition of chlorine.* The 1:3-diene (2·0 g, b.p. 72°) and chlorine (1·5 g) were sealed in a hard-glass tube which was irradiated with ultra-violet light for 18 hr. The mixture was poured into aqueous sodium metabisulphite, separated, dried (P_2O_5), and distilled to give 1:2:3:4-*tetrachloroheptafluoro*cyclo*hexane* (2·63 g), b.p. 197–199°, m.p. 55° (Found: C, 20·8; H, 0·4. Calc. for $C_6HCl_4F_7$: C, 20·7; H, 0·3%).

(c) *Spectroscopy.* Two bands were shown in the infra-red, at 1682 and 1743 cm^{-1}. In the ultra-violet there was a band at (max.) λ2540 Å, ε (approx.) 3720 (*c*, 0·027 g/l. in ethanol).

*Characterisation of the heptafluoro*cyclo*hexa*-1:3-*diene of b.p.* 76°

(a) *Oxidation.* This afforded tetrafluorosuccinic acid, as the dianilinium salt (49 per cent), m.p. 224–225° (Found: C, 50·8; H, 4·1%; equiv., 189), and the di-(*S*-benzylthiuronium) salt m.p. 186–187° (Found: C, 45·8; H, 4·0%).

(b) *Addition of chlorine.* Carried out as before, this gave, as a colourless liquid, a 1:2:3:4-*tetrachloroheptafluoro*cyclo*hexane* (74 per cent), b.p. 184–185° (Found: C, 20·1; H, 0·3%).

(c) *Spectroscopy.* Two bands were shown in the infra-red, at 1679 and 1732 cm^{-1}, and one in the ultra-violet at (max.) λ2625 Å, ε (approx.) 3070 (*c*, 0·086 g/l. in ethanol).

Characterisation of 3H/4H-*octafluoro*cyclo*hex*-1-*ene*

(a) *Oxidation.* The olefin (1·8 g), potassium permanganate (15 g), sodium bicarbonate (3 g), and water (50 cc) were heated at 85° for 16 hr in a rocking autoclave. Treatment as usual gave an acidic solid (1·67 g). Distillation of part (0·22 g) of this at 160–170° (bath temp.)/15 mm onto a cold finger gave the hygroscopic DL-threo-2H:3H-*hexafluoroadipic acid* (0·18 g), m.p. 126–128° (Found: C, 28·1; H, 1·8%; equiv., 125. Calc. for $C_6H_4O_4F_6$: C, 28·4; H, 1·6%; equiv., 127). The crude acid (0·29 g) in water (pH 4) was treated with aqueous *S*-benzylthiuronium chloride to give the *di-*(S-*benzylthiuronium*) salt (0·11 g) (from water), m.p. 226–227° (Found: C, 45·0; H, 4·2; F, 19·6. Calc. for $C_{22}H_{24}O_4N_4S_2F_6$: C, 45·0; H, 4·1; F, 19·4%).

This acid and its derivatives were not very stable, and attempts to prepare a dianilinium salt and a diamide failed. In the former case, a sticky solid was obtained: in the latter, fluoride ion was eliminated, and a product of wide melting-range formed.

(b) *Addition of chlorine.* The olefin (1·97 g), treated as before, gave, as a colourless liquid, 1H:2H-3:4-*dichloro-octafluoro*cyclo*hexane* (1·81 g), b.p. 143–144° (Found: C, 23·4; H, 0·5. Calc. for $C_6H_2Cl_2F_8$: C, 24·3; H, 0·7%).

(c) *Dehydrofluorination.* The olefin (2·23 g, no impurities were detectable in analytical gas chromatography), potassium hydroxide (10 g) and water (10 cc) were boiled together for 8 hr. After being washed with water and dried ($MgSO_4$), the product (1·34 g) showed 3 peaks in analytical gas chromatography (conditions as before), with retention times the same as those of authentic samples of the two conjugated dienes and hexafluorobenzene. Separation (1·19 g) in the preparative-scale column gave heptafluoro*cyclo*hexa-1:3-diene (0·72 g), b.p. 72°; the position isomer (0·26 g) b.p. 76°; and hexafluorobenzene (0·14 g), b.p. 80°. These three compounds had infra-red spectra identical over the range 650–3500 cm^{-1} with those of the authentic samples described before.

(d) *Spectroscopy.* The olefin had a band in the infra-red at 1749 cm^{-1}, but no selective absorption in the ultra-violet between 2400 and 3000 Å.

Oxidative degradation of DL-Threo-2H:3H-*hexafluoroadipic acid*

The acid (1·0 g), potassium permanganate (5·0 g), and aqueous potassium hydroxide (30 cc; 1N) were refluxed together for 22 hr. Isolation as usual afforded tetrafluorosuccinic acid (73 per cent), m.p. 112–114° (cited value[8] 115–116°) (Found: equiv., 97. Calc. for $C_4H_2O_4F_4$: equiv., 95), characterised also as the dianilinium salt (50 per cent over-all), m.p. 225–226° (from acetone–chloroform) (Found: C, 51·0; H, 4·3%; equiv., 189).

Characterisation of 4H/5H-*octafluorocyclohex*-1-*ene*

(a) *Oxidation*. The olefin (2·16 g) was oxidised as usual[11] (at 100°, with no bicarbonate) to give an acidic solid (1·21 g). Distillation of a portion (0·44 g) at 180° (bath temp.)/15 mm onto a cold finger gave the hygroscopic DL-3H:4H-*hexafluoroadipic acid* (0·37 g), m.p. 150–151° (Found: C, 28·2; H, 1·7%; equiv., 126). In a second experiment, the same crude acid (10·5 g) was formed from the olefin (10·4 g).

The acid gave a *dianilinium* salt (56 per cent) (from acetone–chloroform) m.p. 186–187° (Found: C, 49·1; H, 3·9. Calc. for $C_{18}H_{18}O_4N_2F_6$: C, 49·1; H, 4·1%), and a *di-(S-benzylthiuronium)* salt (27 per cent) (from water), m.p. 227–228° (Found: C, 45·4; H, 4·3%).

The crude acid (0·25 g), ethyl alcohol (10 cc), and fluorosulphonic acid (0·5 cc) were refluxed together for 2 hr, the mixture poured into water, and the oily diester extracted with ether. The extracts were separated, dried ($MgSO_4$), filtered, and ammonia passed through for ½ hr. After 15 hr at 10–15°, the ether was distilled off, and the residue recrystallised from water to give the *diamide* (0·08 g), m.p. 206–207° (Found: C, 28·7; H, 2·5. Calc. for $C_6H_6O_2N_2F_6$: C, 28·6; H, 2·4%).

(b) *Addition of chlorine*. 1H:2H-4:5-*Dichlorooctafluorocyclohexane* (54 per cent), a colourless liquid, b.p. 138–139° (Found: C, 23·3; H, 0·6; F, 50·8. Calc. for $C_6H_2Cl_2F_8$: C, 24·3; H, 0·7; F, 51·2%), was obtained by the usual process.

(c) *Dehydrofluorination*. The olefin (6·0 g), potassium hydroxide (10·0 g) and water (10 cc) were refluxed together for 12 hr. The product was separated, washed, and dried ($MgSO_4$). Analytical gas chromatography showed three components, with retention times corresponding to those of 1H-heptafluoro*cyclo*hexa-1:4-diene, hexafluorobenzene, and the starting material. Separation (4·26 g) by preparative-scale gas chromatography gave the diene (1·66 g), b.p. 67°; hexafluorobenzene (0·54 g), b.p. 80°; and the 4H/5H-ene (1·74 g), b.p. 90°. Over the range 650–3500 cm^{-1} these compounds had infra-red spectra identical with those of authentic specimens.

(d) *Spectroscopy*. There was an infra-red band at 1750 cm^{-1}, but no selective absorption in the ultra-violet.

Oxidative degradation of DL-3H:4H-*hexafluoroadipic acid*

The acid (1·19 g) potassium permanganate (5 g) and aqueous potassium hydroxide (30 cc; 1N) were refluxed together for 19 hr to give an acidic solid (0·95 g). A portion (0·69 g) was distilled at 155° (bath temp.)/15 mm onto a cold finger to give difluoromalonic acid (0·61 g) m.p. 115–116° (cited[8] value 117–118°) (Found: equiv., 71·6. Calc. for $C_3H_2O_4F_2$: equiv., 70·0). The crude acid (0·27 g) gave dianilinium difluoromalonate (0·41 g), m.p. 164–165° (Found: C, 55·2; H, 4·9%; equiv., 164).

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Optical resolution of DL-3H:4H-*hexafluoroadipic acid*

A solution of the racemic acid (5·0 g) in ethyl alcohol (100 cc) was added to a solution of L-brucine (15·5 g) in ethyl alcohol (200 cc), and the mixture was boiled, filtered, and set aside. Since a syrup was deposited, the alcohol was evaporated at 15 mm pressure, and the solid residue remaining was dissolved in hot water (100 cc). After 3 days at 10–15° the precipitate (5·61 g) was filtered off from the mother liquor (A) and recrystallised twice from water (25–35 cc) (optical rotation then constant) to give the less soluble diastereoisomeric *di-brucine* salt (3·87 g), m.p. 250° (decomp.) (the specimen softened and water was lost at ca. 185°), $[\alpha]_D^{20} - 12{\cdot}6°$ (*c*, 2·05 in ethanol) (Found: C, 56·8; H, 5·8. Calc. for $C_{52}H_{56}O_{12}N_4F_6$. $3H_2O$: C, 56·9; H, 5·7%).

Concentration of the original mother liquor (A) gave more solid which was filtered off from the new mother liquor (B) and recrystallised five times to give a further crop (1·51 g) of the same diastereoisomer, $[\alpha]_D^{20} - 12{\cdot}5°$ (*c*, 2·08 in ethanol).

A solution of this salt (5·03 g) in warm water (50 cc) was treated with aqueous sodium hydroxide (0·025 N) until just alkaline, and the precipitated brucine (recovery 95 per cent) filtered off. The filtrate was acidified (H_2SO_4) and extracted continuously with ether, the extract dried ($MgSO_4$) and evaporated, to give an acidic solid (1·08 g). Distillation of a portion (0·94 g) at 220–230° (bath temp.)/15 mm onto a cold finger gave the *laevo*-acid (0·66 g) which had $[\alpha]_D^{24} - 17{\cdot}5°$ (*c*, 4·0 in water). The *laevo*-acid (0·20 g) was characterised as the *di-*(*S-benzylthiuronium*) salt (0·19 g) (from water), m.p. 227–228°, $[\alpha]_D^{24} - 10{\cdot}9°$ (*c*, 1·28 in methanol) (Found: C, 45·1; H, 4·1%).

The mother liquor (B) was concentrated further, and the second diastereoisomeric brucine salt was purified to constant rotation by a systematic fractional crystallisation in which the crops of solid obtained were recrystallised from a mother liquor from which a salt of higher negative rotation had been gained. The more soluble diastereoisomeric *di-brucine* salt (3·15 g) had m.p. 250° (decomp.); (with softening at ca. 195°) $[\alpha]_D^{21} - 1{\cdot}94°$ (*c*, 2·05 in ethanol) (Found: C, 57·1; H, 5·7%).

Treatment of this salt (2·81 g) as before gave a crude acid (0·75 g), part (0·60 g) of which was distilled to afford the *dextro*-acid (0·43 g), $[\alpha]_D^{22} + 16{\cdot}6°$ (*c*, 1·93 in water). The *di-*(*S-benzylthiuronium*) salt had m.p. 227–228° (from water), $[\alpha]_D^{24} + 9{\cdot}0°$ (*c*, 1·33 in methanol) (Found: C, 45·1; H, 4·1%).

Dehydrofluorination of 1H/2H:4H-*nonafluorocyclohexane*

The trihydro-compound (45·0 g, b.p. 101°), potassium hydroxide (75 g) and water (75 cc) were refluxed together for 6 hr. The product (31·5 g) showed 6 peaks in analytical gas chromatography with retention times the same as those of the products (i)–(vi) obtained by dehydrofluorination of the stereoisomeric nonafluoro*cyclo*hexane (b.p. 92°). Preparative-scale gas chromatographic separation of the mixture (8·94 g) afforded the following fractions (after distillation from the traps *in vacuo*): (i) (0·67 g), b.p. 66·5–67·0°; (ii) (2·03 g), b.p. 71·5–72·5°; (iii) (0·69 g), b.p. 76°; (iv) (0·81 g), b.p. 80°; (v) (0·35 g), b.p. 85°; and (vi) (3·90 g), b.p. 89–90°. Each of these fractions (i)–(vi) had an infra-red spectrum (over the range 650–3500 cm^{-1}) identical with that of the fraction of similar number isolated from the dehydrofluorination of the nonafluoro*cyclo*hexane, b.p. 92°.

Comparative dehydrofluorinations of the two nonafluorides

A sample (ca. 1 g) of each of the 1H:2H:4H-nonafluoro*cyclo*hexanes (b.p. 92° and 101°) together with 2N-aqueous potassium hydroxide (ca. 10 cc) was shaken in a sealed tube at 45° for ½ hr. The products were analysed by gas chromatography (dinonyl phthalate/kieselguhr 1 : 2, temp. 77°, N_2 flow-rate 1·0 l/hr and tricresyl-phosphate/kieselguhr 1 : 3, temp. 85°, N_2 flow rate 0·9 l./hr; the first packing does not completely separate the 1H:4H/2H-isomer (b.p. 92°) from the 3H/4H-olefin, the second packing does not completely separate the 1H:4H/2H-isomer and the 4H/5H-olefin, but with a run on each packing a complete analysis may be obtained). The 1H:4H/2H-isomer (b.p. 92°) gave very little of the mono-enes and only traces of the dienes, most of the compound being unattacked. Well over half of the 1H/2H:4H-isomer (b.p. 101°) was decomposed. Considerable quantities of the mono-enes were formed, but only small amounts of the dienes.

Reaction of 4H/5H-*octafluoro*cyclo*hex*-1-*ene with lithium aluminium hydride*

The olefin (5·02 g) in diethyl ether (25 cc) was added dropwise during 10 min to a stirred suspension of lithium aluminium hydride (0·88 g) in ether (25 cc) at 0°. After 10 min further, water (25 cc) was added cautiously, followed by sulphuric acid (25 cc, 50 per cent by vol.). The ether layer was separated, dried ($MgSO_4$), and the bulk of the ether distilled off through a 1 ft distillation column packed with gauze spirals. The residue, b.p. >34°, in analytical gas chromatography showed 3 peaks (besides that due to ether). These had retention times of 31, 57, and 62 min (6 ft column, dinonyl phthalate/kieselguhr 1 : 2, temp. 99°, N_2 flow-rate 1·0 l./hr). By means of the preparative-scale gas chromatography column (temp. 103°, N_2 flow-rate 9·2 l./hr) three fractions were obtained: (i) ether; (ii) 1H, 4H/5H-*heptafluoro*cyclo*hex*-1-*ene* (1·63 g), a colourless liquid, b.p. 103–104°, n_D^{18} 1·3503 (Found: C, 34·8; H, 1·5. Calc. for $C_6H_3F_7$: C, 34·6; H, 1·45%); (iii) a mixture of two hexafluoro*cyclo*hexenes (1·64 g), b.p. 117–119° (Found: C, 38·0; H, 2·2. Calc. for $C_6H_4F_6$: C, 37·9; H, 2·1%). This was not completely separated under these conditions, and further separation was not attempted.

The heptafluoro-olefin had a C=C band in the infra-red at 1710 cm^{-1}; over the range 650–3500 cm^{-1} the spectrum was identical with that of a heptafluoro*cyclo*-hexene obtained from the dehydrofluorination of a 1H:2H:4H:5H-octafluoro*cyclo*-hexane,[4] b.p. 119°.

Oxidation of 1H, 4H/5H-*heptafluoro*cyclo*hex*-1-*ene*

Treatment with aqueous permanganate at 85° for 17 hr, followed by working-up as usual, afforded dianilinium DL-3H:4H-hexafluoroadipate (23 per cent), m.p. 189–190° (Found: C, 48·8; H, 4·1%; equiv., 222) and the di-(*S*-benzylthiuronium) salt, m.p. 226–227° (Found: C, 44·9; H, 4·2%).

Dehydrofluorination of 1H, 4H/5H-*heptafluoro*cyclo*hex*-1-*ene*

The olefin (2·92 g) was refluxed for 2½ hr with potassium hydroxide (4·5 g) in water (4·5 cc). The organic layer was separated, washed with water, and dried ($MgSO_4$). Analytical gas chromatography showed 4 peaks, and preparative-scale chromatography afforded 4 fractions; (i) (0·16 g), and (ii) (0·05 g) were hexafluoro-*cyclo*hexa-1:4-dienes; (iii) was pentafluorobenzene (0·48 g), b.p. 89°; and (iv) was

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starting material (1·15 g), b.p. 103–104°. These compounds had infra-red spectra respectively identical with those of the four analogous products[4] from the dehydrofluorination of 1H:2H:4H:5H-octafluoro*cyclo*hexane, b.p. 119°.

Infra-red Spectra

These have been measured[6,7] for all the new compounds described, and the spectra deposited in the Documentation of Molecular Spectra issued by Butterworths. Measurements were made in the vapour state in a 10·1 cm cell over the range 650–3000 cm^{-1}.

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SYNTHESIS OF BENZO-FURAN DERIVATIVES—I

KARANJ KETONE, KARANJIN AND PONGAPIN

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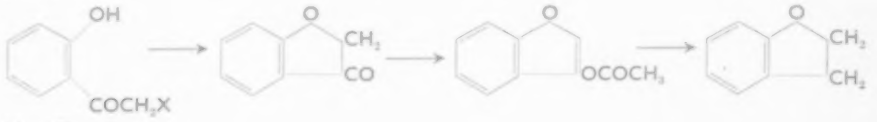
Abstract—A new method of preparing benzo-furan derivatives using substituted allyl phenols has been worked out. Ozonolysis of the allyl derivatives and subsequent ring closure of the resulting *o*-hydroxy-acetaldehydes by means of *o*-phosphoric acid give good yields of karanj ketone, karanjin, pongapin and the corresponding 2-methyl furanochromone. As an alternative route oxidation of the allyl phenol in two stages using performic acid followed by periodic acid has been successfully employed in the synthesis of karanjin.

Two general methods have been extensively used in the past, for constructing a furan ring on a benzene ring, in connexion with the syntheses of naturally occurring benzo-furan derivatives and especially the furano benzo-pyrones. The first starts from an *o*-hydroxy aldehyde and follows the steps shown below:[1]

R = —CH_3 or —C_2H_5

The main difficulty in this method seems to be the lack of availability of the required *o*-hydroxy aldehyde system particularly when the furan unit has to be built up on an already available pyrone system. Frequently it is also difficult to prepare the carbethoxy methyl ether of a hydroxyl group which is *o*-*o*′-disubstituted. Another very serious difficulty which has been experienced in adopting the method for the synthesis of angular furanopyrones[2] (e.g. karanjin) is the decarboxylation of the intermediate furan-5′-carboxylic acid at the last stage. Though successful recently,[3(a),3(b)] it gives extremely poor yields. The second method consists in the cyclisation of an *o*-hydroxy-*ω*-halo acetophenone and converting the resulting coumaran-3-one into a coumaran by the reduction of the enol acetate as shown below:[4]



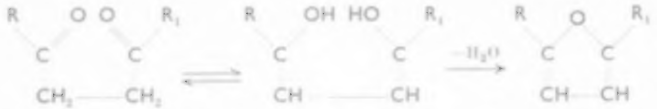
X = Cl or Br

The coumaran thus obtained has to be dehydrogenated to the furan at the last stage and this frequently leads to very poor yields.

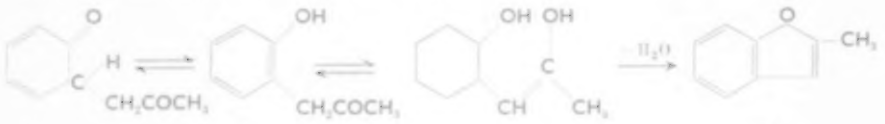
1 A. Rössing *Ber. Dtsch. Chem. Ges.* **17**, 2988 (1884); R. C. Elderfield *Heterocyclic Compounds* Vol. II, p. 14. Wiley, New York (1951).
2 S. Rangaswami and T. R. Seshadri *Proc. Ind. Acad. Sci.* A **9**, 259 (1939).
3(a) L. R. Row and T. R. Seshadri *Proc. Ind. Acad. Sci.* A **33**, 168 (1951).
3(b) L. R. Row and T. R. Seshadri *Proc. Ind. Acad. Sci.* A **34**, 187 (1951).
4 R. L. Shriner and J. Anderson *J. Amer. Chem. Soc.* **60**, 1418 (1938).

Since the benzo–furan system is present in a large number of naturally occurring compounds, many of them having important drug activity, attempts have been made in this laboratory to develop newer methods of building up the furan ring starting from more easily available intermediates. One such successful method is reported in this paper.

Ring closure involving *cyclo*-dehydration of 1:4-dicarbonyl compounds represents one of the oldest and most convenient methods for the preparation of furan derivatives.[5]

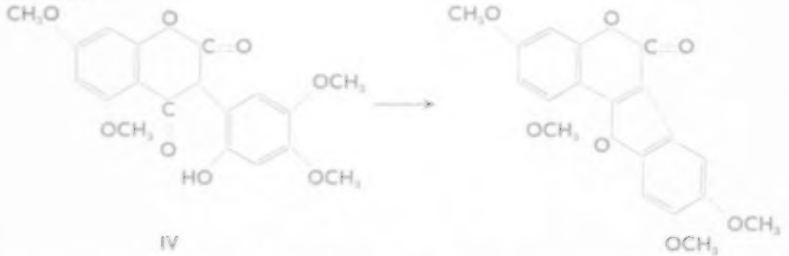


The method is capable of wide application and appears to be limited only by the availability of the requisite dicarbonyl compounds. An *o*-hydroxy phenyl acetone (II) is in effect the mono-enolic form of the 1:4-dicarbonyl compound (I) and yields benzofuran derivative (III) on *cyclo*dehydration.



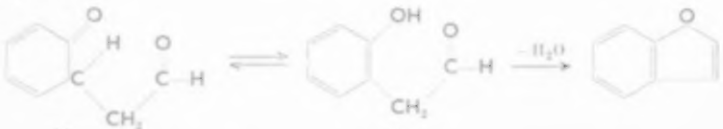
I II III

Preparation of 2-methyl-5 nitro coumarone from 2-hydroxy-5-nitro phenyl acetone is the earliest known example of such a synthesis.[6] More recently similar intermediates (IV) have been employed for the syntheses of compounds containing fused benzo–furan nuclei.[7]



IV

For the synthesis of a simple unsubstituted benzo–furan system the required 1:4-dicarbonyl derivative would be (V) of which the mono-enol form is *o*-hydroxy phenyl acetaldehyde (VI).



V VI

[5] C. Paal *Ber. Dtsch. Chem. Ges.* **17,** 2765 (1884).
[6] W. J. Hale *Ber. Dtsch. Chem. Ges.* **45,** 1596 (1912).
[7] T. R. Govindachari, K. Nagarajan and P. C. Parthasarathy *J. Chem. Soc.* 548 (1957); W. J. Bowyer, A. Robertson and W. B. Whalley *J. Chem. Soc.* 542 (1957).
See also J. N. Chatterjea *Experientia* XII/10, 371 (1956); J. N. Chatterjea and S. K. Roy *J. Ind. Chem. Soc.* **34,** 98 (1957).

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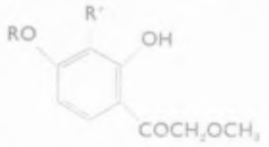
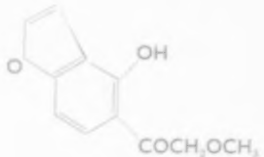
The *o*-hydroxy phenyl acetaldehyde derivatives required for the present work have been prepared from the corresponding *o*-hydroxy allyl compounds by two well-known methods. The first and the better one is the ozonolysis of the allyl compound. Alternatively the allyl double bond is hydroxylated by performic acid and the resulting *vic*-glycol cleaved by periodic acid. Cyclisation of these intermediate acetaldehydes have been most successfully accomplished by means of hot *o*-phosphoric acid which also served as suitable solvent for the reaction.

The first case, where this method was quite successful, was the synthesis of a benzofuran derivative, karanj ketone (X). This is a fission product of karanjin (XIV) and was earlier synthesised from *y*-resorcylic aldehyde (itself difficult to prepare) involving about eight steps giving low yields.[8] In the present method the required allyl intermediate was 2:4-dihydroxy-3-allyl-*o*-methoxy acetophenone (VIII) which was most conveniently prepared by the Claisen migration of the partial allyl ether of *o*-methoxy resacetophenone (VII). The constitution of the product is based on analogy with the related resacetophenone derivative studied earlier by Baker and Lothian.[9] Ozonolysis of the allyl derivative (VIII) proceeded very satisfactorily in ethyl acetate solution, excess of ozone being employed. Catalytic hydrogenation of the ozonide in the same solvent yielded *o*-methoxy resacetophenone-3-acetaldehyde (IX) in excellent yield. Cyclisation of it by *o*-phosphoric acid gave a quantitative yield of karanj ketone (X).





VII R = $-CH_2-CH=CH_2$; R' = H
VIII R = H; R' = $-CH_2-CH=CH_2$
IX R = H; R' = $-CH_2-CHO$

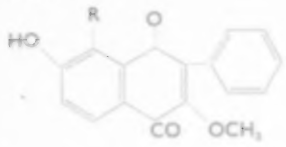
X

In order to test the suitability of this method for building up a furan ring on a flavone unit the synthesis of karanjin (XIV) was next attempted. Karanjin, which occurs in *Pongamia glabra*, is one of the earliest known furano-flavones. Its constitution was established by Limaye[10(a)] and by Manjunath *et al.*[10(b)] and later it was synthesised by Seshadri *et al.*[3(a)] from 3-methoxy-7-hydroxy flavone-8-aldehyde (XI) in poor yields. After a number of trials in the course of the present work the most suitable solvent for ozonolysis of the required intermediate 3-methoxy-7-hydroxy-8-allyl flavone (XII) was found to be formic acid. The main difficulty in this case was the low solubility of the hydroxy allyl compound in the usual solvents employed for ozonolysis. Excess of ozone in this case had to be avoided since the pyrone double-bond is also susceptible and it was found always safer to leave the reaction incomplete and remove the unchanged allyl compound (reduced, in the subsequent step, to the corresponding propyl compound) at a later stage. The intermediate acetaldehyde (XIII) could not, therefore, be obtained pure and was characterised by forming a derivative. It was directly used for cyclisation in the next step giving a good yield of

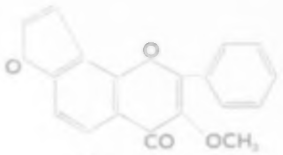
[8] T. R. Seshadri and V. Venkateswarlu *Proc. Ind. Acad. Sci.* A **13**, 404 (1941).
[9] W. Baker and (Miss) O. M. Lothian *J. Chem. Soc.* 628 (1935).
[10(a)] D. B. Limaye *Abs. Ind. Sci. Congress* 151 (1926).
[10(b)] B. L. Manjunath, A. Seetharamiah and S. Siddapa *Ber. Dtsch. Chem. Ges.* **72**, 93 (1939).

karanjin (XIV). Experiments using the more soluble acetate of the allyl flavone led to the fission of the pyrone ring during ozonolysis, the only isolable product being benzoic acid.

Because of the limitations of the ozonolysis in this case, the second route was also explored. Oxidation of the acetate of the hydroxy allyl flavone (XII) using performic acid and subsequent alkaline hydrolysis of the formic ester gave a fair (60 per cent) yield of the corresponding 1:2 diol (XV). Oxidative degradation of the diol (XV) in alcoholic solution with periodic acid gave the required acetaldehyde (XIII) which could not be crystallised but was directly cyclised to karanjin. Yields in this oxidation, however, were not good and on the whole the first method was preferable.

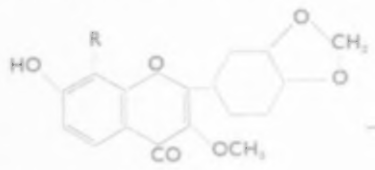


XI R = —CHO
XII R = —CH_2—CH—CH_2
XIII R = —CH_2—CHO
XV R = —CH_2—CHOH—CH_2OH



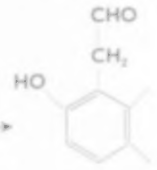
XIV

As a more complex naturally occurring furano–flavone, pongapin (XVIII) has also been synthesised. It occurs in the Australian plant *Pongamia pinnata* L. Merr and was earlier synthesised from karanj ketone.[11] For the present synthesis 3-methoxy-7-hydroxy-3′:4′-methylenedioxy-8-allyl flavone (XVIa) was ozonised in formic acid solution and the resulting aldehyde (XVII), on cyclisation, yielded pongapin (XVIII). The extremely poor solubility of the hydroxy allyl flavone even in formic acid caused some difficulty and success could be achieved by working with dilute solutions. Here also use of excess of ozone or a soluble derivative like the acetate caused oxidation of the pyrone double bond yielding piperonylic acid. Attempts to use the second route in this case were not successful.

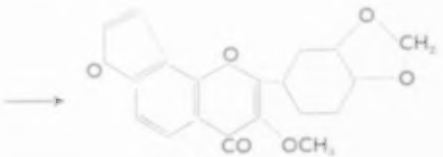


XVI

(a) R = —CH_2—CH—CH_2
(b) R = —CH_2—CHOH—CH_2OH



XVII

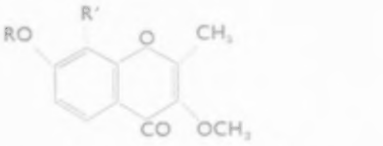


XVIII

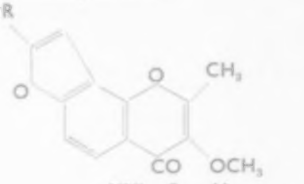
The synthesis of the related simple 2-methyl furano–chromone (XXI) was next done following the same general procedure. This chromone (XXI) is not naturally

[11] L. R. Row *Aust. J. Sci. Res.* A **5**, 754 (1952).

occurring but it was synthesised earlier by the Kostanecki acetylation of karanj ketone by Manjunath *et al.*[12] Ozonolysis of the *o*-hydroxy allyl chromone (XIX) in formic acid and cyclisation of the resulting 8-acetaldehyde (XX) (characterised as the 2:4-dinitrophenyl hydrazone) yielded the furano–chromone (XXI). An attempt was made to prepare an authentic sample of it starting from the readily available 2-methyl-3-methoxy-7-hydroxy chromone-8-aldehyde (XXII) and following the bromacetic ester method. The hydroxy aldehyde (XXII) gave the corresponding carbethoxy methyl ether (XXIII) when heated with bromacetic ester and potassium bicarbonate in acetone solution. Use of potassium carbonate led to the formation of a potassium salt which remained unchanged even after long boiling. The strong acid nature of the 7-hydroxyl group in the compound is worth mentioning; the substance is soluble in sodium bicarbonate just like carboxylic acids.[13] The carbethoxy methyl ether (XXIII) was cyclised to the furan-5′-carboxylic acid (XXIV) by means of sodium ethoxide in alcoholic solution. Decarboxylation of it using both quinoline–copper powder and sodium acetate–acetic anhydride methods, however, yielded only resinous substances from which no pure product could be isolated. The required authentic sample of the chromone (XXI) was, therefore, made from karanj ketone.



XIX R = H; R′ = $-CH_2-CH=CH_2$
XX R = H; R′ = $-CH_2-CHO$
XXII R = H; R′ = $-CHO$
XXIII R = $-CH_2\cdot COO\,Et$; R′ = $-CHO$



XXI R = H
XXIV R = $-COOH$

EXPERIMENTAL

2-Hydroxy-4-allyloxy-o-methoxy acetophenone (VII). A solution of *o*-methoxy resacetophenone (5·8 g) in dry acetone (150 cc), containing allyl bromide (2·8 cc), was refluxed with potassium carbonate (10 g) for 5 hr. Evaporation of the filtered solution and fractionation of the residual brownish oily liquid gave the following: (a) recovered material (1·0 g) obtained as the sodium carbonate soluble fraction, (b) 2-hydroxy-4-allyloxy-*o*-methoxy acetophenone (3 g), a pale yellow viscous liquid, obtained as the sodium hydroxide soluble fraction (2:4-dinitrophenyl hydrazone, crimson plates from alcohol, m.p. 174–5°C. Found: C, 53·9; H, 4·8: Calc. for $C_{18}H_{18}O_7N_4$: C, 53·7; H, 4·5%), (c) 2:4-diallyloxy-*o*-methoxy acetophenone (0·5 g), a colourless oily liquid, as the sodium hydroxide insoluble fraction (2:4-dinitrophenyl hydrazone, orange plates from alcohol, m.p. 132–3°C. Found: C, 57·0; H, 5·0. Calc. for $C_{21}H_{22}O_7N_4$: C, 57·0; H, 5·0%).

Refluxing the mixture for a longer time did not improve the yield of the partial allyl ether, more of the diallyl ether being formed.

2:4-Dihydroxy-3-allyl-o-methoxy acetophenone (VIII). The partial allyl ether (3 g) underwent smooth Claisen migration when kept for 2 hr at 190–95° under reduced pressure. The migrated product (2 g) was isolated as the sodium carbonate soluble fraction. It crystallised from dilute alcohol as colourless long needless melting at

[12] B. L. Manjunath and A. Seetharamiah *Ber. Dtsch. Chem. Ges.* **72**, 97 (1939).
[13] See also K. Aghoramurthy and T. R. Seshadri *J. Chem. Soc.* 3065 (1954).

139–39·5° (Found: in a sample dried at 100° in vacuum: C, 64·9; H, 6·1; Calc. for $C_{12}H_{14}O_4$: C, 64·9; H, 6·3%).

2:4-*Dihydroxy-ω-methoxy acetophenone-3-acetaldehyde* (IX). A stream of ozonised oxygen (2%; 150 cc/min) was passed through a cooled (−15°C) solution of the above allyl ketone (0·5 g) in dry ethyl acetate (100 cc) till excess of ozone could be detected in the outlet (approx. 30 min). The ozonide was decomposed by shaking the solution with hydrogen in the presence of palladium–charcoal (5%; 1 g) till one mole of the gas was absorbed. The filtered solution on evaporation yielded the acetaldehydo–ketone (0·3 g). It crystallised from a mixture of ethyl acetate and petroleum ether as colourless stout needles, m.p. 133–133·5° (Found: C, 59·3; H, 5·2 Calc. for $C_{11}H_{12}O_5$: C, 58·9; H, 5·4%). Its aqueous solution reduced Tollens' reagent in the cold and its dimedone derivative crystallised from dilute alcohol as colourless plates, m.p. 182–3°.

Cyclisation of (IX) to *4-hydroxy-5-ω-methoxyacetyl coumarone* (X). A solution of the aldehydo–ketone (0·15 g) in *o*-phosphoric acid (2 cc) was heated in a boiling water bath for 10 min and then poured over crushed ice when a colourless solid separated out. This was extracted with benzene (200 cc), the benzene solution partially concentrated and the concentrate percolated through a short column of activated alumina. The column was washed with fresh benzene (500 cc). The percolate and the washings were mixed together and evaporated to dryness; the residual colourless solid (0·1 g) crystallised from dilute alcohol as rectangular plates, m.p. 96–97° alone or when mixed with an authentic sample of karanj ketone prepared from karanjin. Its acetate, prepared by boiling with acetic anhydride and pyridine, came out of alcohol as colourless hexagonal plates, m.p. 99–100° alone or when mixed with an authentic sample.

3-Methoxy-7-hydroxy flavone-8-acetaldehyde (XIII). A stream of ozonised oxygen (4%; 150 cc/min) was passed through a solution of 3-methoxy-7-hydroxy-8-allyl flavone[14] (XII) (0·5 g) in formic acid (50 cc) at 10° for 20 min (the optimum time being found after a number of experiments). The solution was allowed to warm up to room temperature and then shaken with hydrogen in the presence of palladium–charcoal (5%; 0·5 g) until the absorption of hydrogen (approximately 1 mol) ceased. The filtered solution was diluted with ice-water and extracted with chloroform; the extract was washed with ice cold aqueous sodium bicarbonate solution. Evaporation of the solvent yielded the aldehyde as a pale yellow viscous mass which could not be crystallised. It gave a 2:4-dinitrophenyl hydrazone derivative which crystallised from chloroform–alcohol as yellow thin needles, m.p. 220–21° (Found: C, 58·8; H, 3·9. Calc. for $C_{24}H_{18}O_8N_4$: C, 58·8; H, 3·7%).

Cyclisation of (XIII) *to karanjin* (XIV). A solution of the above aldehyde (from 0·5 g. of the allyl flavone) in *o*-phosphoric acid (10 cc) was kept stirred at 120° for 15 min, then cooled and poured on crushed ice. The colourless solid that separated was dissolved in chloroform and the solution chromatographed on a column of activated alumina (50 g). Elution of the column with benzene and evaporation of the solvent yielded karanjin (0·2 g), colourless needles from methanol, m.p. 157–8° alone or when mixed with a sample obtained from *Pongamia glabra*.[15]

[14] B. Krishnaswamy and T. R. Seshadri *Proc. Ind. Acad. Sci.* A **13**, 43 (1941).
[15] D. B. Limaye *Abs. Ind. Sci. Congress* 118 (1925); N.V.S. Rao, J. V. Rao and T. R. Seshadri *Proc. Ind. Acad. Sci.* A **10**, 65 (1939).

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Further elution of the alumina column with alcohol gave 3-methoxy-7-hydroxy-8-propyl flavone (0·15 g) as colourless long needles, m.p. 235–6°. Mixed melting point with a sample obtained from 3-methoxy-7-hydroxy-8 allyl flavone (XII) by catalytic reduction was undepressed (Found: C, 73·9; H, 5·9. Calc. for $C_{19}H_{18}O_4$: C, 73·5; H, 5·8%). Its acetate crystallised from alcohol as colourless hairy needles, m.p. 110–11°.

3-*Methoxy*-7-*hydroxy*-8-(*β*:*γ*-*dihydroxypropyl*) *flavone* (XV). A solution of 3-methoxy-7-acetoxy-8-allyl flavone (0·5 g) in anhydrous formic acid (5 cc) was treated with hydrogen peroxide (2 cc; 30% excess) and the mixture maintained at 40°C for 2 hr. It was then diluted with water (200 cc) and extracted with chloroform (200 cc). The extract was washed with ice cold sodium bicarbonate solution, dried and evaporated. The residual glassy solid could not be crystallised and was, therefore, hydrolysed by keeping a solution of it in aqueous methanolic sodium hydroxide (5%; 5 cc) for 15 min at room temperature. Acidification with dilute hydrochloric acid yielded the diol (0·3 g). It crystallised from dilute alcohol as colourless aggregates of small prisms, m.p. 208–10° (Found: C, 66·6; H, 5·4. Calc. for $C_{19}H_{18}O_6$: requires C, 66·7; H, 5·3%).

Periodic acid oxidation of the diol (XV). The diol (0·1 g) was dissolved in alcohol (35 cc) and treated with periodic acid solution (5 cc; 1·6%). After 6 hr at room temperature with occasional stirring, the mixture was diluted with water (100 cc) and extracted with chloroform. The extract was washed with a solution of sodium sulphite, dried and evaporated. The residual viscous oily material could not be crystallised but gave positive aldehyde test. It was directly cyclised and the product purified in the previous manner yielding karanjin (65 mg) identical with the sample described earlier.

3-*Methoxy*-3′:4′-*methylenedioxy*-7-*hydroxy flavone*-8-*acetaldehyde* (XVII). Ozonolysis of 3-methoxy-3′:4′-methylenedioxy-7-hydroxy-8-allyl flavone[16] (XVI,a) (0·25 g) in anhydrous formic acid (120 cc) at 10°C for 0·5 hr and working up as described earlier yielded the aldehyde as a viscous liquid. It was characterised as the 2:4-dinitrophenyl hydrazone which crystallised as orange prisms form alcohol, m.p. 225–6° (Found: C, 55·9; H, 3·8. Calc. for $C_{25}H_{18}O_{10}N_4$: C, 56·2; H, 3·4%).

Cyclisation of (XVII) *to pongapin* (XVIII). Cyclisation of the crude aldehyde (from 0·25 g allyl flavone) by means of *o*-phosphoric acid as previously described, gave a mixture. Separation of it by chromatography over alumina (10 g) yielded (a) pongapin (50 mg) in the benzene eluent as pale yellow needles from alcohol, m.p. 190–91° alone or when mixed with an authentic sample and (b) 3-methoxy-3′:4′-methylenedioxy-7-hydroxy-8-propyl flavone (40 mg) in the alcohol eluent, as colourless rods from alcohol, m.p. 275–6°. Mixed m.p. of (b) with an authentic sample of the same propyl flavone obtained by the catalytic hydrogenation of the allyl flavone (XVI,a) was undepressed (Found: C, 67·4; H, 5·4. Calc. for $C_{20}H_{18}O_6$: C, 67·8; H, 5·1%).

3-*Methoxy*-3′:4′-*methylenedioxy*-7-*hydroxy*-8-(*β*:*γ*-*dihydroxypropyl*) *flavone* (XVI,b). A solution of 3-methoxy-3′:4′-methylenedioxy-7-acetoxy-8-allyl flavone (0·5 g) in formic acid (15 cc) was treated dropwise with hydrogen peroxide (20 cc; 30%). The mixture was kept at 40°C for 2 hr and then diluted with water. Extraction of the clear aqueous solution with chloroform, washing the extract with aqueous sodium

[16] S. S. Chibber, A. K. Ganguli, S. K. Mukerjee and T. R. Seshadri *Proc. Ind. Acad. Sci.* **47**, 19 (1957).

bicarbonate and evaporation yielded a glassy solid. This was dissolved in methanol (10 cc), the solution treated with aqueous potassium hydroxide (20 cc; 10%) and the mixture kept warm (60°) for 15 min. Acidification with dilute hydrochloric acid yielded the diol (0·4 g). It crystallised from alcohol as pale yellow rods m.p. 225–6° (Found: C, 62·5; H, 4·8. Calc. for $C_{20}H_{18}O_8$: C, 62·2; H, 4·7%).

2-*Methyl*-3-*methoxy*-7-*hydroxy chromone*-8-*acetaldehyde* (XX). Ozonisation of a cooled solution of 2-methyl-3-methoxy-7-hydroxy-8-allyl chromone[17] (XIX) (0·5 g) in formic acid (100 cc) for 0·5 hr and subsequent catalytic hydrogenation of the ozonide yielded the aldehyde as a viscous yellow liquid. Its 2:4-dinitrophenyl hydrazone came out of alcohol as clusters of orange plates, m.p. 249–50° (Found: C, 52·8; H, 3·7. Calc. for $C_{19}H_{16}O_8N_4$:C, 53·3; H, 3·7%).

2-*Methyl*-3-*methoxy furano*-(2′:3′-7:8)-*chromone* (XXI). Heating the crude aldehyde (from 0·5 g of the allyl chromone) with *o*-phosphoric acid (10 cc) at 100° for 15 min and separating the resulting mixture in the usual manner yielded (a) the furanochromone (0·2 g) as colourless rectangular plates from methanol, m.p. 153–4° alone or when mixed with an authentic sample, (b) 2-methyl-3-methoxy-7-hydroxy-8-propyl chromone (0·1 g) as colourless long needles from alcohol, m.p. and mixed m.p. with a sample, prepared from the allyl chromone by catalytic reduction, 216–18° (Found: C, 67·8; H, 6·7. Calc. for $C_{14}H_{16}O_4$: C, 67·7; H, 6·5%). Its acetate, obtained from ethyl acetate as colourless stout rhombs, melted at 103–4°C.

2-*Methyl*-3-*methoxy*-7-*carbethoxymethoxy chromone*-8-*aldehyde* (XXIII). This was prepared earlier by Rangaswami and Seshadri[2] but the following modified method gives better yields. A solution of 2-methyl-3-methoxy-7-hydroxy chromone-8-aldehyde[18] (XXII) (1·0 g) in acetone (75 cc) containing excess of ethyl bromoacetate (2·5 cc) was refluxed with dry potassium bicarbonate (6 g) for 10 hr. It was then filtered, concentrated and cooled. The solid (0·9 g) that separated was filtered and washed with petroleum ether till free from bromacetic ester. On recrystallisation from alcohol, it was obtained as pale yellow plates, m.p. 176–7° alone or when mixed with a sample described by earlier workers.

2-*Methyl*-3-*methoxy*-5′-*carboxy furano*-(2′:3′-7:8)-*chromone* (XXIV). A mixture of the above carbethoxy methyl ether (1 g) and sodium ethoxide from (0·1 g of sodium) in absolute alcohol (100 cc) was shaken vigorously for about 30 min at room temperature during which time the colour of the suspension changed to deep yellow. Cooling and treating the mixture with dry ether precipitated the sodium salts which were then dissolved in water and acidified when the furan 5′-carboxylic acid (0·5 g) separated as a yellow solid. It came from alcohol as small yellow prisms, m.p. 309–11° (d.) (Found: C, 57·5; H, 4·3. Calc. for $C_{14}H_{10}O_6$: C, 57·5; H, 4·1%).

[17] S. Rangaswami and T. R. Seshadri *Proc. Ind. Acad. Sci.* **9**, 4 (1937).
[18] S. Rangaswami and T. R. Seshadri *Proc. Ind. Acad. Sci.* **9**, 7 (1939).

Tetrahedron, 1958, Vol. 2, pp. 211–240. Pergamon Press Ltd., London

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SYNTHESE DES IMMUNSPEZIFISCHEN, POLYPEPTID-ARTIGEN HAPTENS DER ANTHRAX-SUBTILIS BACILLEN-GRUPPE. EIN SYNTHETISCHER BEWEIS DER KONSTITUTION DER NATÜRLICHEN POLYGLUTAMINSÄUREN*

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(*Received* 22 *July* 1957)

Zusammenfassung—Es wurde die Synthese der γ-Poly-L-glutaminsäure (IIIa), γ-Poly-D-glutaminsäure (IIIb) und der *mesoiden* γ-Poly-glutaminsäure (IIIc) durchgeführt.

Als Schlüsselsubstanz der Synthese diente der γ-Glutamyl-glutaminsäure-αα′-dimethylester (I) der L-L-Form (Ia), D-D-Form (Ib) bzw. L-D-Form (Ic); diese drei Startdipeptide wurden aus L- bzw. D-Glutaminsäure in mehreren Schritten aufgebaut. Die intermolekulare Polyacylierung der bifunktionellen Startdipeptide, die zur Bildung des γ-Poly-glutaminsäure-α-methylesters (II) der entsprechenden Konfiguration führte, liess sich auf viererlei Weise—durch Aktivierung der Carboxyl- bzw. Aminogruppe—bewirken. Nach der alkalischen Verseifung der Polyester (II) wurden die entsprechenden γ-Poly-glutaminsäuren über ihre schwerlöslichen Kupfer(II)-salze abgesondert und durch Dialyse gereinigt.

Der chemische und der von Prof. G. Ivánovics durchgeführte serologische Vergleich der γ-Polyglutaminsäuren verschiedener Konfiguration mit dem Anthrax-Polypeptid und dem Subtilis-Polypeptid brachte—in Übereinstimmung mit der früher mittels Abbau durchgeführten Konstitutionsermittlung—den Beweis, dass das Anthrax-Polypeptid die Konstitution der γ-Poly-D-glutaminsäure innehat. Da ausser der γ-Poly-D-glutaminsäure auch die *mesoide* γ-Polyglutaminsäure mit Antianthrax-Immunseren eine Präzipitationsreaktion zeigte, ist es nicht ausgeschlossen, dass in den Peptidketten des Subtilis-Polypeptids D- und L-γ-Glutamylreste vergesellschaftet vorkommen.

Durch die Synthese der γ-Poly-D-glutaminsäure (=Anthrax-Polypeptid) wurde zum ersten Mal die Vollsynthese eines natürlichen Haptens verwirklicht.

Abstract—γ-Poly-L-glutamic acid (IIIa), γ-poly-D-glutamic acid (IIIb) and *mesoid* γ-poly-glutamic acid (IIIc) have been synthesised.

The syntheses started from αα′-dimethyl γ-glutamyl-glutamate of either the L-L-form (Ia) or the D-D-form or the L-D-form, respectively, prepared from the corresponding glutamic acid stereoisomer in a series of consecutive steps. The directed intermolecular polyacylation of these bifunctional dipeptides to α-methyl γ-polyglutamates (II) of the respective configuration has been effected by activation either of the carboxyl or of the amino group, in altogether four different ways. The polyester so forming has then been hydrolysed with aqueous alkali, and the polyacid—isolated in form of its copper (II) salt—was purified after foregoing demetalation by carefully conducted dialysis.

The synthetic stereoisomers of γ-poly-glutamic acid have then been compared with the anthrax polypeptide and subtilis polypeptide. The γ-poly-D-glutamic acid proved to be identical in any respect with the anthrax polypeptide, and was found (by Prof. G. Ivánovics) to give a precipitation reaction with antianthrax horse immune serum. Since the *mesoid* γ-poly-glutamic acid was likewise found to produce a precipitate in this reaction it appears that the subtilis polypeptide may contain peptide chains composed of units of both the L- and the D-form of glutamic acid.

The synthesis of γ-poly-D-glutamic acid (=anthrax polypeptide) represents the first total synthesis of a natural hapten.

* Vorläufige Mitteilungen: *Naturwissenschaften* **42**, 210 (1955); **42**, 463 (1955); **44**, 89 (1957).

ZUR PROBLEMSTELLUNG

Vor geraumer Zeit haben Ivánovics und Bruckner[1] über die Isolierung der immunspezifischen Substanz der Milzbrandbacillenkapsel berichtet und gezeigt, dass diese Substanz ein biuretnegatives Polypeptid darstellt, das bei der salzsauren Hydrolyse in hoher Ausbeute D(−)-Glutaminsäure-hydrochlorid liefert. Gleichzeitig wurde auch gefunden, dass verschiedene grampositive, aërobe, mesophile Sporenträger (z. B. *B. subtilis*, früher als *B. mesentericus* bezeichnet) eine Substanz in ihren Nährboden ausscheiden, die sich besonders leicht isolieren lässt; sie schien mit der spezifischen Kapselsubstanz der Milzbrandbacillen (*B. anthracis*) identisch zu sein. Es sollen im folgenden diese zwei Polypeptide als Anthrax-Polypeptid (APP) bzw. als Subtilis-Polypeptid (SPP) bezeichnet werden.

Spätere Untersuchungen[2,3] haben den strengen Beweis erbracht, dass beide Polypeptide nur aus Glutaminsäureresten aufgebaut sind, d.h. monotone Polypeptide darstellen, wie dies unmittelbar nach ihrer ersten Untersuchung[1,4] bereits vermutet wurde. Man hat auch bewiesen, dass das APP eine D-konfigurative Einheitlichkeit besitzt[3,5] (sie ist also eine optisch reine Poly-D-glutaminsäure), hingegen scheint das SPP, das aus dem Nährboden der auf die ursprüngliche Art[1] gezüchteten *B. subtilis* Stämme abgetrennt werden kann, etwa 85% D-isomere und 15% L-isomere Glutaminsäurereste zu enthalten.[5] Unlängst wurde sogar gefunden,[6] dass das Mengenverhältnis der D- und L-isomeren Bausteine beim SPP sehr stark von der Züchtungsart ein und desselben *B. subtilis* Stammes abhängt, so dass die Menge der eingebauten L-Glutaminsäurereste fallweise auch 80% betragen kann. Nun wurden SPP Präparate, deren Gehalt an L-Glutaminsäureresten 15–20% stark überwiegt, bisher serologisch nicht geprüft. Hingegen ist festgestellt worden, dass das nach dem ursprünglichen Verfahren[1] gewinnbare SPP eine ebenso ausgeprägte serologische Reaktion aufweist wie das APP: Die Lösungen beider Polypeptide zeigen mit Antianthrax-Immunseren bis zu einer Verdünnung von $3{,}2 \times 10^6$ eine Präzipitationsreaktion.[1] Nach den immunbiologischen Untersuchungen ist das APP und ebenso auch das (nach dem ursprünglichen Verfahren[1] gewinnbare) SPP als immunspezifisches Hapten (Halbantigen) der Anthrax-Subtilis Bacillengruppe zu betrachten.

Aus den Ergebnissen eines speziellen Abbaus, dem das APP und das SPP unterworfen wurde, konnte man darauf schliessen, dass beide Polypeptide γ-Poly-glutaminsäuren (III) darstellen.[7] Die Zuverlässigkeit dieser Aussage wurde vorerst durch den analogen Abbau des synthetisch gewonnenen α-Poly-L-glutaminsäure-γ-methylesters und seines D-Antipoden auf indirekte Weise bewiesen: Es liess sich das für die α-Glutamylbindung charakteristische Abbauprodukt, die αγ-Diaminobuttersäure (in Form ihres Diflavianats) fassen, während das für die γ-Glutamylbindung charak-

[1] G. Ivánovics und V. Bruckner *Naturwissenschaften* **25**, 250 (1937); *Z. ImmunForsch.* **90**, 304 (1937); **91**, 175 (1937).
[2] M. Bovarnick *J. Biol. Chem.* **143**, 415 (1942); G. Pongor *Experientia* **6**, 421 (1950).
[3] W. E. Hanby und H. N. Rydon *Biochem. J.* **40**, 297 (1946).
[4] V. Bruckner, G. Ivánovics und M. Kovács Oskolás *Magy. Chem. Fölv.* **45**, 131 (1939); V. Bruckner und M. Kovács Oskolás *Acta Chem. et Phys. Univ. Szeged* **1**, 144 (1943).
[5] D. W. Watson, W. J. Cromartie, W. L. Bloom, R. J. Heckly, W. J. McGhee und N. Weissman *J. Infect. Dis.* **80**, 121 (1947); M. Torii *Med. J. Osaka Univ.* **6**, 725 (1955); **6**, 1043 (1956).
[6] C. B. Thorne, C. G. Gómez, H. E. Noyes und R. D. Housewright *J. Bact.* **68**, 307 (1954).
[7] J. Kovács und V. Bruckner *Research* **5**, 194 (1952); *J. Chem. Soc.* 4255 (1952); V. Bruckner, J. Kovács und H. Nagy *J. Chem. Soc.* 148 (1953); V. Bruckner, J. Kovács, K. Kovács und H. Nagy *Experientia* **9**, 63 (1953); V. Bruckner, J. Kovács und G. Dénes *Nature, Lond.* **172**, 508 (1953); V. Bruckner, J. Kovács und I. Kandel *Naturwissenschaften* **40**, 243 (1953); V. Bruckner, J. Kovács, I. Kandel und G. Dénes *Hung. Acta Chim.* **7**, 223 (1955).

teristische Abbauprodukt, die β-Formylpropionsäure weder präparativ (z.B. als *p*-Nitrophenylhydrazon), noch chromatographisch nachgewiesen werden konnte.[8,9] Unlängst konnte auch ein direkter Beweis für die Brauchbarkeit des konstitutionsermittelnden Abbaus geliefert werden, und zwar an Hand des synthetisch zugänglichen[10] α,γ-Poly-L-glutaminsäure-methylesters, der dadurch gekennzeichnet ist, dass sich in seiner Peptidkette α- und γ-Glutamylbindungen laufend abwechseln. Hier konnten in der Tat beide erwarteten Abbauprodukte präparativ gefasst werden.

Für die Konstitutionsermittlung des APP's und des SPP's war es ausschlaggebend, dass sich die synthetischen α-Poly-glutaminsäuren nicht nur durch das Ergebnis ihres speziellen Abbaus, sondern auch in ihren Eigenschaften (d.h. sehr schlechte Löslichkeit in Wasser, positive Biuretreaktion, Racemisierung in alkalischer Lösung, keine serologische Reaktion) vom APP bzw. SPP sehr charakteristisch unterschieden. Es war somit die Aussage von Hanby und Mitarbeitern,[3, 11] dass nämlich das APP vorwiegend (dasjenige ursprünglicher Isolierungsart[1] sogar ausschliesslich nur) α-Glutamylbindungen enthielte, widerlegt worden.

Als letzten Schritt des Konstitutionsbeweises haben wir jetzt die Synthese des APP's, d.h. der γ-Poly-D-glutaminsäure (IIIb) durchgeführt, nachdem der am besten geeignete Weg vorerst in der L-Reihe aufgesucht wurde.[12, 13] Gleichzeitig mit den letztgenannten Vorarbeiten und unabhängig von uns hat auch Waley[14] die Synthese der γ-Poly-L-glutaminsäure (IIIa) verwirklicht. Als Schlüsselsubstanz der Synthese bediente sich Waley desselben Dipeptidderivats wie wir (s. unten: L-L-Startdipeptid; Ia); auch wurden beim Aufbau des letzteren prinzipiell die gleichen Wege eingeschlagen. Ausser der γ-Poly-glutaminsäure der D- und der L-Reihe haben wir auch die Synthese der γ-Poly-(γ-L-glutamyl-D-glutaminsäure) (IIIc) verwirklicht. Dieser Typ der stereoisomeren γ-Poly-glutaminsäuren, der schlechthin als *mesoide* γ-Poly-glutaminsäure (IIIc) bezeichnet werden kann, ist dadurch gekennzeichnet, dass sich in seiner Peptidkette L- und D-γ-Glutamylreste laufend abwechseln. Dieses Produkt war besonders zum Vergleich mit dem SPP bestimmt.

ALLGEMEINER WEG DER SYNTHESEN

Die Synthese der oben aufgezählten drei stereoisomeren γ-Poly-glutaminsäuren gestaltete sich folgendermassen. Zuerst wurde der γ-Glutamyl-glutaminsäure-αα′-dimethylester (I) der entsprechenden sterischen Reihe aufgebaut; diese drei stereoisomeren Dipeptidderivate werden in folgendem als L-L-Startdipeptid (Ia), D-D-Startdipeptid (Ib) bzw. L-D-Startdipeptid (Ic) bezeichnet. Nun wurden die bifunktionellen Startdipeptide durch vorherige Aktivierung ihrer Carboxylgruppe bzw. Aminogruppe einer zur Bildung des γ-Poly-glutaminsäure-α-methylesters (II) führenden intermolekularen Polyacylierung unterworfen. Diese Umsetzung wurde in möglichst konzentriertester Lösung bewirkt, um die Wahrscheinlichkeit der Bildung von *cyclo*Peptiden

[8] J. Kovács, V. Bruckner und K. Kovács *J. Chem. Soc.* 145 (1953); V. Bruckner, J. Kovács und K. Kovács *J. Chem. Soc.* 1512 (1953).
[9] V. Bruckner, K. Kovács und J. Kovács *Hung. Acta Chim.* **3**, 361 (1953); V. Bruckner, K. Kovács, J. Kovács und A. Kótai *Experientia* **10**, 166 (1954); *Hung. Acta Chim.* **5**, 267 (1955).
[10] V. Bruckner, M. Szekerke und J. Kovács *Naturwissenschaften* **43**, 107 (1956); *Z. Physiol. Chem.* **309**, 25 (1957).
[11] W. E. Hanby, S. G. Waley und J. Watson *J. Chem. Soc.* 3239 (1950); H. N. Rydon *Biochemical Society Symposium* No. 1, p. 42. Cambridge (1948); E. J. Ambrose *J. Chem. Soc.* 3246 (1950).
[12] V. Bruckner, J. Kovács, H. Nagy und M. Kajtár *Hung. Acta Chim.* **6**, 219 (1955); vorläufige Mitt: *Naturwissenschaften* **41**, 528 (1954).
[13] V. Bruckner, J. Wein, H. Nagy, M. Kajtár und J. Kovács *Naturwissenschaften* **42** 210 (1955).
[14] S. G. Waley *J. Chem. Soc.* 520 (1955); *Chem. & Ind. (Rev.)* 1148 (1954).

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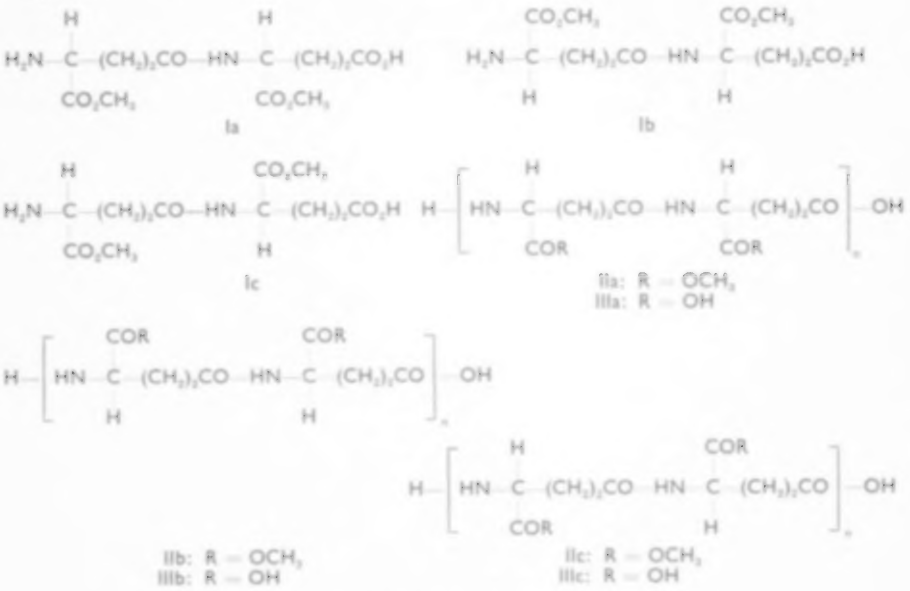
zu vermindern. Formal betrachtet dürfte angenommen werden, dass im Polyester die endständige Carboxyl- bzw. Aminogruppe noch in ihrer aktivierten Form vorliegt (vgl. z.B. die Formeln XVI, XXI und XXX), doch werden im Laufe der Herstellung der freien Polysäuren aus den entsprechenden Polyestern derartige Gruppen wieder zu freien Carboxyl- bzw. Aminogruppen umgewandelt. Zur Herstellung der freien Polysäure (III) wurde nämlich der Polyester alkalisch verseift, dann die Polysäure zuerst in Form ihres schwerlöslichen Kupfer(II)salzes abgeschieden, aus diesem mit Schwefelwasserstoff freigesetzt, durch Dialyse gereinigt bzw. von den niedrigeren Oligopeptiden befreit und zum Schluss aus der Lösung durch Gefriertrocknung gewonnen. Es ist zu bemerken, dass Polyester, die in Dimethylformamid-Lösung hergestellt worden sind und die dieses Lösungsmittel stark binden, in Wasser löslich sind; dies ermöglichte die Einschaltung einer Dialyse gegen Wasser auch schon beim Polyester.



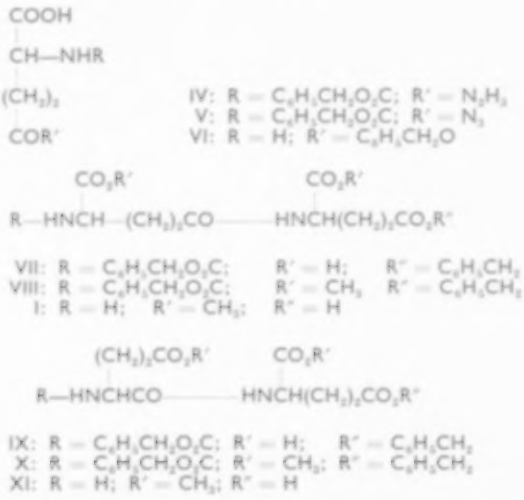
SYNTHESE DER STEREOISOMEREN STARTDIPEPTIDE

Über die Synthese des L-L-Startdipeptids, d.h. des γ-L-Glutamyl-L-glutaminsäure-αα′-dimethylesters (Ia) haben wir[12] und unabhängig von uns auch Waley[11] bereits ausführlich berichtet. Einige unterschiedliche Beobachtungen werden an Hand der analogen Synthese des D-D-Startdipeptids (Ib) angegeben.

Die Synthese des D-D-Startdipeptids, d.h. des γ-D-Glutamyl-D-Glutaminsäure-αα′-dimethylesters (Ib), die der Synthese des L-L-Startdipeptids (Ia) genau nachgebildet war, nahm folgenden Weg. Carbobenzoxy-D-glutaminsäure-γ-hydrazid (IV) wurde über das (nicht isolierte) Azid (V) mit D-Glutaminsäure-γ-benzylester (VI) zum Carbobenzoxy-γ-D-glutamyl-D-glutaminsäure-γ′-benzylester (VII) gekoppelt. Das unmittelbar anfallende kristalline Produkt war erwartungsgemäss[13] mit wenig Carbobenzoxy-α-D-glutamyl-D-glutaminsäure-γ′-benzylester (IX) verunreinigt, der sich auch

[11] H. Sachs und E. Brand *J. Amer. Chem. Soc.* **75**, 4608, 4610 (1953).

durch wiederholtes Umkristallisieren nicht vollständig entfernen liess. Diese Beobachtung, die selbstredend auch für das vollkommen analog aufgebaute L-L-Produkt VII zustimmt,[12] steht im Gegensatz zu der Beobachtung von Waley,[14] der darüber berichtete, dass bei der Umsetzung des L-Säureazids V mit dem L-Benzylester VI zum Derivat VII des L-L-Startdipeptids das strukturisomere L-L-Derivat IX nicht mitentsteht bzw. im kristallin anfallenden Umsetzungsprodukt nicht enthalten ist. Trotz der erwähnten geringen Verunreinigung des Produktes VII konnte die Synthese erfolgreich weitergeführt werden. Es folgte nämlich als nächster Schritt die Umsetzung des Produktes VII (in Methanol-Lösung) mit Diazomethan zum Carbobenzoxy-γ-D-glutamyl-D-glutaminsäure-αα′-dimethyl-γ′-benzylester (VIII), der gleich kristallin anfiel und aus Methanol sehr gut umkristallisiert werden konnte, wobei das Umsetzungsprodukt der strukturisomeren Komponente, der Carbobenzoxy-α-D-glutamyl-D-glutaminsäure-γα′-dimethyl-γ′-benzylester (X), fast ganz in den Mutterlaugen zurückblieb. Die Hydrogenolyse (Pd-Tierkohle, Methanol) des Derivates VIII lieferte schliesslich den γ-D-Glutamyl-D-glutaminsäure-αα′-dimethylester, d.h. das D-D-Startdipeptid (Ib), dessen papierchromatographische Untersuchung darauf hinwies, dass die Beimengung der strukturisomeren Verbindung XI höchstens 0,5% beträgt. Wie auch Waley[14] fand, enthält das kristalline L-L-Startdipeptid (Ia) 1 Mol. Kristallwasser.[12] Wir haben in Gegensatz zu Waley festgestellt, dass man das


COOH
CH—NHR
(CH2)2
COR′
IV: R = C6H5CH2O2C; R′ = N2H3
V: R = C6H5CH2O2C; R′ = N3
VI: R = H; R′ = C6H5CH2O
CO2R′
CO2R′
R—HNCH—(CH2)2CO—HNCH(CH2)2CO2R″
VII: R = C6H5CH2O2C; R′ = H; R″ = C6H5CH2
VIII: R = C6H5CH2O2C; R′ = CH3; R″ = C6H5CH2
I: R = H; R′ = CH3; R″ = H
(CH2)2CO2R′
CO2R′
R—HNCHCO—HNCH(CH2)2CO2R″
IX: R = C6H5CH2O2C; R′ = H; R″ = C6H5CH2
X: R = C6H5CH2O2C; R′ = CH3; R″ = C6H5CH2
XI: R = H; R′ = CH3; R″ = H

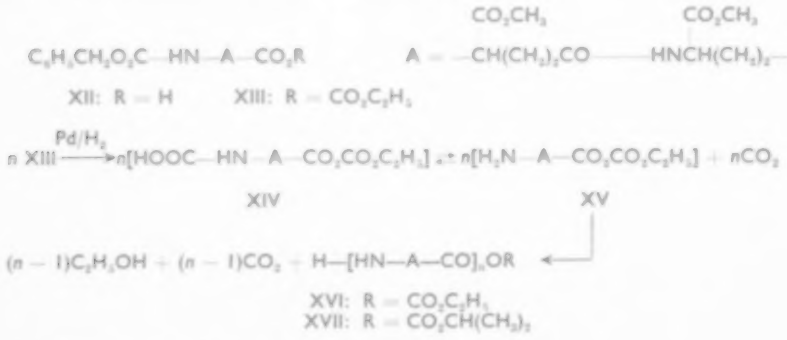
Kristallwasser durch einfaches Trocknen—es sei denn in der Vakuumpistole bei mässiger Temperatur—nicht ohne sekundäre Veränderung der Substanz entfernen kann.[12] Es ist selbstredend, dass dies auch für das D-D-Startdipeptid (Ib) zutrifft.

Auf die oben geschilderte Weise wurde auch das L-D-Startdipeptid, d.h. der γ-L-Glutamyl-D-glutaminsäure-αα′-dimethylester (Ic) aufgebaut; der erste Schritt bestand aus der Umsetzung des aus dem Carbobenzoxy-L-glutaminsäure-γ-hydrazid (IV) frisch bereiteten L-Azids (V) mit D-Glutaminsäure-γ-benzylester (VI) zum Carbobenzoxy-γ-L-glutamyl-D-glutaminsäure-γ′-benzylester (VII). Sämtliche Zwischenprodukte waren auch hier—mit Ausnahme des nicht isolierten L-Azids (V)—gut kristallisierende Verbindungen.

UMSETZUNG DER STEREOISOMEREN STARTDIPEPTIDE ZU γ-POLY-GLUTAMINSÄURE-α-METHYLESTERN (II) DEN ENTSPRECHENDEN STEREOISOMEREN FORMEN

Die zum Polyester (II) führende intermolekulare Polyacylierung der bifunktionellen Startdipeptide (I) konnte nach Umsetzung der Carboxyl- bzw. Aminogruppe zu einer reaktionsfähigeren Gruppe leicht bewirkt werden. Diese Aktivierung, die fallweise gleich mit der intermolekularen Umsetzung verbunden war, erfolgte beim L-L-Startdipeptid (Ia) auf viererlei Weise (Methoden 1–4). Auf das kostspieligere D-D-Startdipeptid (Ib) und L-D-Startdipeptid (Ic) wurden nur zwei bzw. eine Methode (Methode 2 und 4, bzw. Methode 2) übertragen.

(1) *Die erste Methode* stellt eine sinngemässe Abänderung eines bereits mitgeteilten Verfahrens[12] dar: Aus dem L-L-Startdipeptid (Ia) wurde zuerst der Carbobenzoxy-γ-L-glutamyl-L-glutaminsäure-αα′-dimethylester (XII) bereitet und dieser in eiskalter Dimethylformamid-Lösung nach der Methode von Boissonnas[16] mit Chlorameisensäureäthylester in Gegenwart von 1 Mol. Triäthylamin zum gemischten Esteranhydrid XIII umgesetzt. Das letztere Produkt wurde gleich in seiner eiskalten Lösung nach Zusatz von Pd-Tierkohle einer Hydrogenolyse unterworfen. Diese wurde nicht im geschlossenen Gefäss, sondern—aus Gründen, die a.a.O.[12] bereits erörtert worden sind—mit durchströmendem Wasserstoff durchgeführt. Die CO_2-Abgabe, die im entweichenden Gas bestimmt wurde, kam bei 1 Mol. nicht zum Stillstand, ein Zeichen dafür, dass unter den gegebenen Versuchsbedingungen nicht nur die Hydrogenolyse der Carbobenzoxygruppe (XIII → XIV → XV) stattfindet, sondern auch schon die intermolekulare Polyacylierung des entstandenen bifunktionellen Derivats XV einsetzt (XV → XVI). Um den letzteren Vorgang zu fördern, wurde—nachdem die CO_2-Abgabe (insgesamt 1,36 Mol.) praktisch beendet war—das Reaktionsgemisch nach Zusatz von 1 Mol. Triäthylamin gelinde erwärmt (60°). Es ist anzunehmen, dass das gemischte Anhydrid XV nicht nur die Acylgruppe des L-L-Startdipeptids (H_2N—*A*—CO—), sondern—wenn auch in geringerem Masse—seine Carbäthoxygruppe an eine Aminogruppe zu übertragen vermag. Im letzteren Falle erleidet jedoch die intermolekulare Polyacylierung einen Abbruch, da die N-Carbäthoxygruppe nicht hydrogenolysiert werden kann. Wenngleich dieser vorzeitige Abbruch der intermolekularen Polyacylierung nicht vermieden werden konnte, zeigten doch die Versuchsergebnisse, dass das polydisperse Umsetzungsprodukt (XVI) auch Komponenten verhältnismässig hohen Molekulargewichtes enthält.



[16] R. A. Boissonnas *Helv. Chim. Acta* **34**, 874 (1951).

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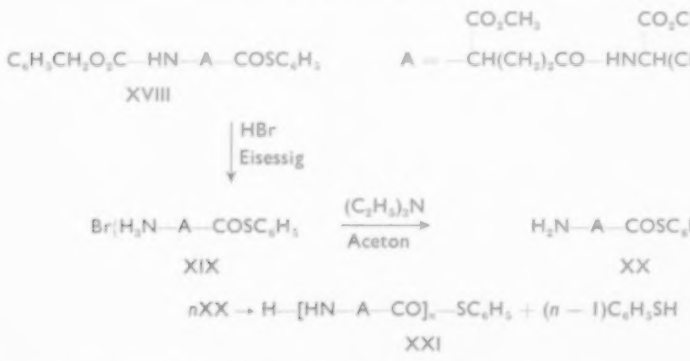
Ausgehend von der Beobachtung von Boissonnas und Schuman,[17] dass die Esteranhydridbildung aus einem Carbonsäureanion und Chlorameisensäureester durch die gleichzeitige Anwesenheit von freien Aminogruppen nur unwesentlich beeinträchtigt wird, liess sich das oben erörterte Verfahren wesentlich vereinfachen, indem auf die vorübergehende Blockierung der Aminogruppe des L-L-Startdipeptids (Ia → XII) zwecks Herstellung des gemischten Esteranhydrids XV verzichtet werden konnte. Die Bildung des Polyesters XVI findet auch dann statt, wenn eine eiskalte Dimethylformamid-Lösung des L-L-Startdipeptids (Ia) zuerst mit 1 Mol. Triäthylamin und 1 Mol. Chlorameisensäureäthylester versetzt (Ia → XV) und dann—nach Zusatz eines zweiten Mol. Triäthylamins—gelinde erwärmt wird (XV → XVI). Es ist zu bemerken, dass nach Abdampfen des Lösungsmittels der Polyester in wasserlöslicher Form gewonnen wurde und somit gegen Wasser dialysiert werden konnte. Um die Wahrscheinlichkeit der N-Carbalkoxylierung in der zweiten Reaktionsphase zu vermindern, wurde in einem anderen Versuch anstatt Chlorameisensäureäthylester der Isopropylester angewant,[18] zugleich wurde hier vor der Reaktion die Dimethylformamid-Lösung des L-L-Startdipeptids (Ic) durch eine azeotrope Destillation mit Toluol entwässert. Die Bildung des Polyesters (XVII) verlief auch hier glatt, doch nahm die Ausbeute nur unwesentlich zu (43,5%, gegen 38,5% d.Th.). Es wurde aber gefunden, dass aus diesem Polyester die durch Dialyse gereinigte freie Polysäure in etwas besserer Ausbeute gewonnen werden konnte (s. Tabelle 2), ein Zeichen dafür, dass dieser Polyester einen grösseren Anteil an höhermolekularen Komponenten enthält.

(2) *Die zweite Methode*, die von der Peptid- bzw. Polypeptidsynthese von Wieland und Bernhard[19] Gebrauch macht, wurde auf alle drei stereoisomeren Startdipeptide übertragen. Demgemäss wurde das Carbobenzoxy-derivat des L-L-, D-D-, bzw. L-D-Startdipeptids (XII aus Ia, Ib bzw. Ic) über das gemischte Anhydrid XIII mit Thiophenol zum Thiophenylester XVIII umgesetzt und aus diesem mit Eisessig-Bromwasserstoff[20] das Hydrobromid des Startdipeptid-thiophenylesters (XIX) bereitet. Wird dessen Aminogruppe mit Triäthylamin in Aceton-Lösung freigesetzt, so erleidet das primär entstehende Produkt XX eine zur Bildung des Polyesters XXI führende intermolekulare Polyacylierung, die durch Erwärmen gefördert werden kann:



[17] R. A. Boissonnas und J. Schuman *Helv. Chim. Acta* **35**, 2229 (1952).
[18] Th. Wieland und H. Bernhard *Liebigs Ann.* **572**, 190 (1951); J. R. Vaughan, Jr. und R. L. Osato *J. Amer. Chem. Soc.* **74**, 676 (1952).
[19] Th. Wieland und H. Bernhard *Liebigs Ann.* **582**, 218 (1953).
[20] D. Ben-Ishai und A. Berger *J. Org. Chem.* **17**, 1564 (1952); R. A. Boissonnas und G. Preitner *Helv. Chim. Acta* **35**, 2240 (1952); R. Schwyzer *Ibid.* **37**, 155 (1954).

(3) *Die dritte Methode* beruhte auf einer Methode, die zuerst Sheehan und Hess[21] bei der Synthese von Di- und Tripeptiden angewandt haben. Wie bekannt, lässt sich nach diesem Verfahren z.B. ein Dipeptid derart herstellen, dass eine Aminosäure mit geschützter (z.B. acylierter) Aminogruppe (XXII) und ein Aminosäureester (XXIII) mit Hilfe von Di*cyclo*hexylcarbodiimid (XXIV) kondensiert wird. Die Reaktion verläuft in Lösung schon bei Raumtemperatur, wobei neben dem Dipeptidderivat (XXV) als Beiprodukt Di*cyclo*hexylharnstoff (XXVI) entsteht:

$$\underset{\text{XXII}}{AcHNCHRCOOH} + \underset{\text{XXIII}}{H_2NCHR'COOC_2H_5} + \underset{\text{XXIV}}{C_6H_{11}N{=}C{=}NC_6H_{11}} \rightarrow$$

$$\underset{\text{XXV}}{AcNHCHRCO{-}HNCHR'COOC_2H_5} + \underset{\text{XXVI}}{(C_6H_{11}NH)_2CO}$$

Der Mechanismus der kondensierenden Wirkung des Di*cyclo*hexylcarbodiimids (und anderer Carbodiimide) konnte Khorana[22] aufklären. Es handelt sich um eine Aktivierung der Carboxylgruppe, deren erste Phase darin besteht, dass das Carbodiimid die Reaktionskomponente mit freier Carboxylgruppe anlagert, wodurch ein O-acyliertes *iso*-harnstoffderivat (XXVIIa) gebildet wird, das schon selbst seine Acylgruppe auf Aminogruppen zu übertragen vermag.

$$\underset{\text{XXVII}}{C_6H_{11}NH{-}C(=NC_6H_{11}){-}OCOQ} \qquad \underset{\text{XXVIII}}{C_6H_{11}NH{-}C(=NC_6H_{11}){-}HN{-}A{-}COOH}$$

a: Q = —CHRNHAc
b: Q = —A—NH_2

Man konnte vermuten, dass sich diese, zur Ausgestaltung einer einzigen Peptidbindung dienende Methode auch zur Polyautokondensation des bifunktionellen Startdipeptids (I) heranziehen liesse, vorausgesetzt, dass die freie Aminogruppe—trotz ihres nukleophilen Stickstoffatoms—die Entstehung des reaktionsfähigen Zwischenproduktes (XXVIIb) nicht in entscheidendem Mass verhindert. Eine derartige Konkurrenzreaktion würde nämlich zur Bildung eines vermutlich stabilen Guanidinderivates (XXVIII) führen und somit einen gänzlichen bzw. vorzeitigen Abbruch des intermolekularen Polyacylierungsvorganges mit sich bringen.

Nun zeigten Modellversuche, die mit Di*cyclo*hexylcarbodiimid und verschiedenen primären Aminen durchgeführt wurden, dass die Bildung von Guanidinderivaten unter den Versuchsbedingungen, die bei der Polyautokondensation der Startdipeptide (I) angewandt wurden (s. unten), kaum vor sich geht. Dies bestätigen auch die Versuche, die mit dem L-L- bzw. D-D-Startdipeptid (Ia bzw. Ib) selbst durchgeführt wurden: löst man in der Dimethylformamid-Lösung des Startdipeptids (I) Di*cyclo*hexylcarbodiimid (XXIV), so erfolgt selbst bei Raumtemperatur schon nach einigen Minuten—als Zeichen einer Polyautokondensation—die kristalline Ausscheidung von Di*cyclo*hexylharnstoff (XXVI):

$$\underset{\text{I}}{n\,H_2N{-}A{-}COOH} + \underset{\text{XXIV}}{m\,C_6H_{11}N{=}C{=}NC_6H_{11}} \rightarrow \underset{\text{II}}{H{-}[HN{-}A{-}CO]_n{-}OH} + \underset{\text{XXVI}}{m(C_6H_{11}NH)_2CO}$$

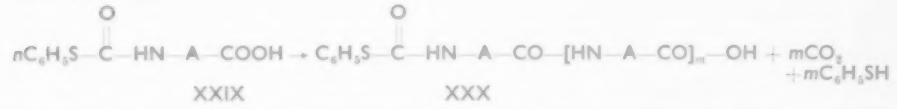
(A wie bei XVIII)

Das Filtrat enthielt den γ-Poly-L-glutaminsäure-α-methylester (IIa) bzw. den γ-Poly-D-glutaminsäure-α-methylester (IIb), der zur entsprechenden Polysäure verarbeitet worden konnte.

[21] J. C. Sheehan und G. P. Hess *J. Amer. Chem. Soc.* **77**, 1077 (1955).
[22] H. G. Khorana *Chem. & Ind. (Rev.)* 1087 (1955).

Es sei hier bemerkt, dass die Carbodiimid-Methode zur Herstellung von monotonen Polypeptiden das erste Mal an Hand der Synthese der αγ-Poly-glutaminsäure erprobt wurde.[10]

(4) *Die vierte Methode* wurde aus der Polypeptidsynthese von Noguchi und Hayakawa[23] entwickelt. Nach dem ursprünglichen Verfahren der japanischen Forscher wird ein Oligopeptidester zuerst mit Chlorthioameisensäure-phenylester ($ClCOSC_6H_5$) zum N-Carbothiophenylderivat umgesetzt, dann die Estergruppe sauer verseift und zum Schluss die Benzol-Pyridin Lösung des N-Carbothiophenyl-oligopeptids (XXIX) erwärmt, wobei die Bildung des Polypeptids (XXX) unter Abspaltung von Kohlendioxyd und Thiophenol vor sich geht. Wie bekannt, handelt es sich hier um die Aktivierung der Aminogruppe; der zum Polypeptid führende Umsatz lässt sich folgend formulieren:



XXIX XXX

Formal betrachtet bildet sich hier ein Polypeptid, dessen (endständige) Aminogruppe carbothiophenyliert vorliegt, doch können solche Gruppen schon durch einen milden alkalischen Eingriff zu freien Aminogruppen regeneriert werden.

Vorversuche zeigten, dass in Gegenwart von Triäthylamin auch eine Carboxylgruppe mit Chlorthioameisensäurephenylester "aktivierbar" ist, wobei zunächst ein gemischtes Anhydrid vom Typ XXXI entstehen dürfte. Es war somit zu erwarten, dass sich das Verfahren von Noguchi und Hayakawa unmittelbar auf das Startdipeptid (I) übertragen liesse, dass also beim Umsatz des Startdipeptids mit Chlorthioameisensäure-phenylester in Gegenwart von Triäthylamin ausser dem N-Carbothiophenyl-Startdipeptid (XXIX; A = wie bei XVIII) auch das gemischte Anhydrid XXXII entstehen kann, das—ebenso wie das N-Carbothiophenyl-Startdipeptid (XXIX)—

XXXI XXXII

einer intermolekularen Polyacylierung fähig wäre. Versuche, die mit dem L-L-Startdipeptid (Ia) durchgeführt wurden, zeigten nun folgendes: wird eine Suspension des L-L-Startdipeptids in eiskaltem, triäthylaminhaltigem Chloroform mit einer nahezu äquimolekularen Menge von Chlorthioameisensäurephenylester versetzt und das Gemisch geschüttelt, so geht ein erheblicher Teil des angesetzten Startdipeptids unter Selbsterwärmung des Gemisches sofort in Lösung. Aus der Lösung lässt sich ein farbloses Produkt ("primäres Umsetzungsprodukt") isolieren; wird die Benzol-Pyridin-Lösung dieser Substanz erwärmt (90°), so erfolgt allmählich die Ausscheidung einer hochmolekularen Substanz, die nach ihren Eigenschaften und analytischen Daten den γ-Poly-L-glutaminsäure-α-methylester (IIa) darstellt.

Da das labile "primäre Umsetzungsprodukt", das vermutlich uneinheitlich ist, bisher einwandfrei nicht definiert werden konnte, haben wir zur Klärung der sich hier abspielenden Reaktionen mit weiteren Untersuchungen begonnen, über die später berichtet werden soll. Einstweilen sei nur bemerkt, dass der ganze Vorgang viel verwickelter ist. Gemischte Anhydride des Typs XXXI sind nämlich nicht zu fassen, da sie sich sofort nach ihrer Entstehung zu Carbonsäureanhydriden (XXXIII)

[23] J. Noguchi und T. Hayakawa *J. Amer. Chem. Soc.* **76**, 2846 (1954).

umlagern. Es ist anzunehmen, dass diese Umlagerung mit einer Disproportionierung verbunden ist die im Sinne der Gleichung XXXI → XXXIII + XXXIV verläuft:

$$\underset{\text{XXXI}}{2RCO_2COSC_6H_5} \rightarrow \underset{\text{XXXIII}}{(RCO)_2O} + \underset{\text{XXXIV}}{[(C_6H_5SCO)_2O]}$$

Das bisher unbekannte Anhydrid XXXIV, dessen Existenzfähigkeit sehr fraglich erscheint, dürfte durch Aminogruppen sofort abgefangen werden, wobei nebst Kohlendioxyd und Thiophenol ein N-Carbothiophenylderivat (Typ XXIX) entstehen müsste. Es wird an anderer Stelle[24] erörtert, welche Vorstellungen man sich über die Zusammensetzung des "primären Umsetzungsproduktes" und über den Mechanismus seiner Umsetzung zum Polyester (IIa) machen kann.

Als Ergänzung zu den oben erörterten vier Methoden sei nochmals darauf hingewiesen, dass unabhängig von uns auch Waley[14] die Synthese des L-L-Startdipeptids (Ia) verwirklicht hat. Es wurde von ihm auch eine Polyautokondensation des L-L-Startdipeptids zum γ-Poly-L-glutaminsäure-α-methylester (IIa) durchgeführt, und zwar mit Hilfe von Tetraäthylpyrophosphit, d.h. nach einer Methode, die zuerst von Anderson *et al.*[25] zu Peptidsynthesen herangezogen wurde. Es ist zu bemerken, dass die γ-Poly-L-glutaminsäure (IIIa), die Waley[14] durch Verseifung des Polyesters gewonnen hat, 0,6% gebundenen Phosphor enthält. Wir haben das Verfahren genau reproduziert und gefunden, dass es weniger befriedigend ist, als die Methoden 1–4. Es sei noch bemerkt, dass Waley bisher weder über die Synthese des D-D-Startdipeptids (Ib) und L-D-Startdipeptids (Ic), noch über deren Polyautokondensation berichtet hat.

VERGLEICHENDER ABBAU DES SYNTHETISCHEN γ-POLY-L-GLUTAMINSÄURE-α-METHYLESTERS

Um einen entsprechenden Vergleich mit dem mit Methanol veresterten APP und SPP zu haben, wurde der nach dem zweiten Verfahren gewonnene γ-Poly-L-glutaminsäure-α-methylester (IIa) mit flüssigem Ammoniak in das entsprechende Polyamid (IIa; R = NH_2 anstatt R = OCH_3) umgewandelt, dann dieses dem Hofmann'schen Abbau unterworfen und danach sofort mit Salzsäure hydrolysiert. Aus dem Hydrolysat konnte β-Formylpropionsäure in Form ihres *p*-Nitrophenylhydrazons isoliert werden, hingegen liess sich das für die α-Glutamylbindung charakteristische Abbauprodukt,[8,9] die αγ-Diaminobuttersäure nicht nachweisen. Wie bekannt,[7] kam man beim gleichen Abbau des aus dem APP oder SPP hergestellten Polymethylesters zu demselben Ergebnis, was als ein Beweis des Vorherrschens der γ-Glutamylbindungen betrachtet wurde.

HERSTELLUNG DER γ-POLY-GLUTAMINSÄUREN AUS DEN ENTSPRECHENDEN POLYESTERN

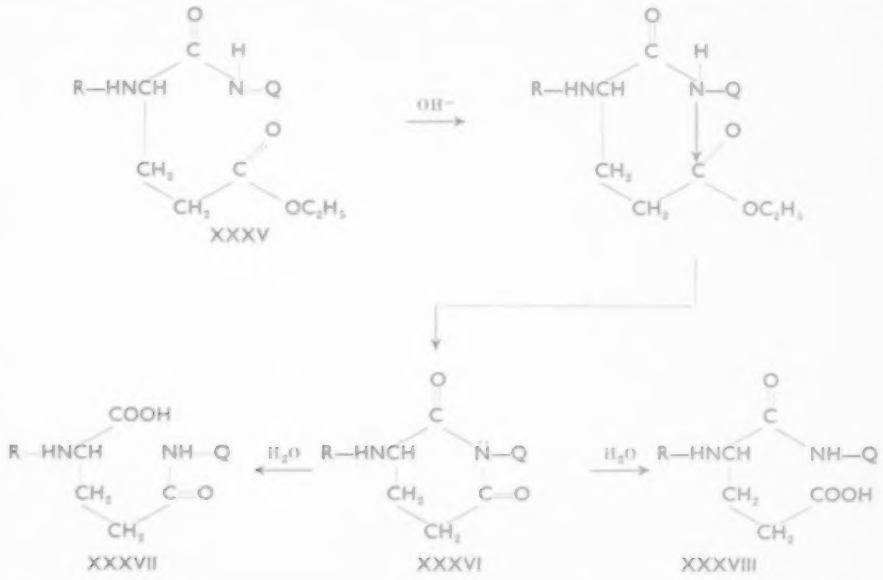
Es wurde bereits erwähnt, dass zwecks Herstellung der freien Polysäuren die auf verschiedenen Wegen gewonnenen Polyester alkalisch verseift und die Polysäuren über ihre schwerlöslichen Kupfer(II)salze isoliert wurden. Man kann damit rechnen, dass im Laufe dieser Operationen auch endständige Carboxyl- und Aminogruppen freigesetzt werden, die im synthetischen Polyester noch blockiert vorliegen dürften (z.B. XVI, XXI, XXX), doch ist eine Regenerierung von Aminogruppen, die im Laufe des dritten Verfahrens Guanidingruppen (Typ XXVIII) etwa anteilig geworden sind, kaum zu erwarten.

Die auf oben angegebene Weise gewonnenen stereoisomeren γ-Poly-glutaminsäuren, d.h. die γ-Poly-L-glutaminsäure (IIIa), γ-Poly-D-glutaminsäure (IIIb) und die

[24] V. Bruckner und J. Kovács *Hung. Acta Chim.* **12**, 363 (1957).
[25] G. W. Anderson, J. Blondiger und A. D. Welcher *J. Amer. Chem. Soc.* **74**, 5309 (1952).

mesoide γ-Poly-glutaminsäure (IIIc), stellen schneeweisse, flaumartige Produkte dar, die in Wasser sehr leicht löslich sind; sie zeigen keine Biuretreaktion und ihre Ninhydrinreaktion ist im Vergleich zur γ-L-Glutamyl-L-glutaminsäure nur sehr schwach positiv (quantitative Angaben s. im Versuchsteil). All diese Eigenschaften kommen auch dem APP und SPP zu.

Es drängt sich hier die Frage auf, ob die alkalische Verseifung der γ-Poly-glutaminsäure-α-methylester etwa nicht von einer innermolekularen, partiellen α → γ-Transpeptidierung begleitet wird. Battersby und Robinson[26] haben nämlich gefunden, dass die alkalische Verseifung des Äthylesters des N-Acetyl-diglycyl-α-L-glutamyl-glycin-hexylamids (Teilformel: XXXV) mit einer weitgehenden α → γ-Transpeptidierung (und vollständigen Racemisierung) verbunden ist, so dass ein Gemisch der strukturisomeren Peptide XXXVII und XXXVIII entsteht, in welchem das Derivat mit γ-Glutamylbindung (XXXVII) sogar vorherrscht. Dieser Vorgang lässt sich so deuten, dass durch einen übergänglichen Ringschluss ein 2:6-Diketopiperidinderivat (XXXVI) entsteht, welches—als sekundäres Säureamid—an zwei verschiedenen Stellen eine hydrolytische Ringsprengung (XXXVII ← XXXVI → XXXVIII) erleidet:



Hierzu sei bemerkt, dass die innermolekulare Transpeptidierung von strukturisomeren Glutamylpeptiden (Typ XXXVII und XXXVIII) mit freier Carboxylgruppe—allerdings mit Hilfe einer anderen Methode—in unserem Institut schon früher durchgeführt wurde,[27] und zwar in beiden Richtungen (α ⇄ γ). Dabei wurden die intermedieren Ringverbindungen (Typ XXXVI) in kristalliner Form gefasst und ihre (auf Einwirkung von verdünnter Lauge) in zwei Richtungen verlaufende hydrolytische Ringöffnung (XXXVII ← XXXVI → XXXVIII) streng bewiesen.[28]

[26] A. R. Battersby und J. C. Robinson *Chem. & Ind. (Rev.)* 45 (1954); *J. Chem. Soc.* 259 (1955).
[27] K. Medzihradszky erörtert in einem Vortrag von V. Bruckner und J. Kovács erschienen in *Magyar Tud. Akadémia VII. Osztályának Közleményei* **3**, 105 (1952).
[28] J. Kovács, K. Medzihradszky und V. Bruckner *Naturwissenschaften* **41**, 450 (1954); *Hung. Acta Chim.* **6**, 183 (1955).

Da nun bei dieser Transpeptidierung nach unserer Erfahrung[28] immer ein Gemisch entsteht, in welchem die γ-Glutamylverbindung (XXXVII) in rund zehnfacher Menge die α-Glutamylverbindung (XXXVIII) überwiegt, so wird man mit einer *weitgehenden* γ → α-Transpeptidierung bei der Verseifung der γ-Poly-glutaminsäure-α-methylester keinesfalls rechnen müssen. Überdies, ist die γ → α-Transpeptidierung hier auch dadurch erschwert, dass bei der Näherung der veresterten Carboxylgruppe eines γ-Glutamylrestes (XXXVII, $COOCH_3$ statt COOH) zum betreffenden Stickstoffatom zwei lange Ketten (R und Q) mitschwingen müssen. Umgekehrt, wird man damit rechnen müssen, dass bei der alkalischen Verseifung eines α-Poly-glutaminsäure-γ-esters (Teilformel: XXXV) die nötige Kettenschwingung leichter erfolgt und somit auch schon aus diesem Grund eine α → γ-Transpeptidierung viel leichter vor sich gehen kann.

In Übereinstimmung mit diesen Folgerungen hat Volcani[29] gefunden, dass ein von ihm isoliertes, γ-L-Glutamylbindungen spezifisch spaltendes Enzym unsere synthetische γ-Poly-L-glutaminsäure (IIIa) bis zu 95% zu L-Glutaminsäure abbaut. Dies kann als ein Beweis dessen betrachtet werden, dass in diesem synthetischen Produkt α-Glutamylbindungen nur in sehr niedrigem Prozentsatz anwesend sein dürften, ferner auch, dass eine nennenswerte Racemisierung im Laufe der Synthese nicht stattgefunden hat.

Übrigens wurde die optische Reinheit einiger unserer Endprodukte auch durch ihre vollständige salzsaure Hydrolyse geprüft; das spezifische Drehungsvermögen der entstandenen Glutaminsäure war nur ein wenig geringer als dasjenige optisch reiner L- bzw. D-Glutaminsäure. Diese Versuche müssen noch mit grösseren Ansätzen wiederholt und auf sämtliche Endprodukte erstreckt werden. Es sei hier gleich bemerkt, dass die nach der zweiten Methode gewonnene γ-Poly-L-glutaminsäure (IIIa) in Wasser den spez. Drehwert $[\alpha]_4^{20} = -23{,}8°$ zeigte, während der spez. Drehwert ihres natürlichen Antipoden (IIIb), d.h. des APP's in Wasser $[\alpha]_D^{20} = +23{,}5°$ beträgt. Diese vorzügliche Übereinstimmung ist kaum als strenger Beweis der optischen Reinheit des synthetischen Produktes zu betrachten, da der spez. Drehwert auch vom Molekulargewicht der Polysäure abhängen dürfte, einwandfreie Molekulargewichtsbestimmungen jedoch noch nicht durchgeführt wurden (s. unten).

Wie bei allen Synthesen hochmolekularer Stoffe, entstanden auch in unseren Fällen polydisperse Produkte. Es wurde darauf Gewicht gelegt, dass aus diesen Gemischen durch andauernde Dialyse—es sei denn auf Kosten der Ausbeute—Präparate je höheren durchschnittlichen Molekulargewichtes abgesondert werden, die papierchromatographisch (Phenol–Wasser) nicht mehr aufgeteilt werden können und fast unbewegt an der Startstelle verbleiben. Zuverlässige Bestimmungen der Molekulargewichte unserer Produkte stehen noch aus, es wurde einstweilen nur aus ihren Aminostickstoffwerten (van Slyke) auf ihr durchschnittliches Molekulargewicht geschlossen, ebenso wie dies früher beim APP und SPP geschah. Die Aminostickstoffwerte unserer synthetischen Endprodukte schwankten—vom Ausmass der Dialyse abhängend, das wegen Materialmangels fallweise eingeschränkt werden musste—zwischen 0,16 und 1,5% (bei der *mesoiden* Polysäure (IIIc) konnte wegen Materialmangels bisher nur ein Präparat vom Aminostickstoffwert 2,9% gewonnen werden), während die Aminostickstoffwerte von APP und SPP Präparaten ursprünglicher

[29] Briefliche Mitteilung von Dr. B. E. Volcani, The Weizmann Institute of Science, Rehovoth, Israel vom 24 Juni (1956).

Isolierungsart[1] eine ziemliche Konstanz (0,18–0,20%) zeigten. Infolge der Spaltung der N-endständigen γ-Glutamylbindung, die bei der van Slyke-schen Bestimmung—wenigstens im Falle von Oligopeptiden—beobachtet wurde,[30] sind die durchschnittlichen Molekulargewichte, die aus den Aminostickstoffwerten berechnet werden, wahrscheinlich bis zur Irrealität nach tieferen Werten hin verzerrt. Welches Ausmass diese Verzerrung erreichen kann, wird an anderer Stelle[21] gezeigt. Trotzdem kann man aber aus den Aminostickstoff-werten der natürlichen Polyglutaminsäuren ursprünglicher Isolierungsart[1] das *Verhältnis* ihrer durchschnittlichen Molekulargewichte einigermassen abschätzen,—vorausgesetzt, dass die van Slyke'sche Bestimmung bei sämtlichen Proben ganz genau unter ein und denselben Versuchsbedingungen durchgeführt wird. Diese vergleichende Abschätzung des relativen Molekulargewichtes ist bei den Naturprodukten deshalb zulässig, weil sie praktisch homodispers sind. Hingegen ist bei den polydispersen synthetischen Produkten dieser Vergleich (es sei denn mit einander, oder mit dem APP bzw. SPP) kaum statthaft, umsomehr da hier das durchschnittliche Molekulargewicht ohne Kenntnis der quantitativen Verteilung der einzelnen Komponenten keinen realen Wert hat. Wenn man jedoch von der etwaigen Anwesenheit von *cyclo*Peptiden absieht, so wird man—ohne einen groben Fehler zu begehen—annehmen können, dass z.B. eine synthetische, polydisperse γ-Poly-glutaminsäure vom Aminostickstoffwert 0,5% (ber. Molekulargewicht 2800) auch Komponenten enthalten dürfte, deren Molekulargewichte dasjenige des Naturproduktes (Aminostickstoffwert 0,2%, ber. Molekulargewicht 7000) schon erreichen. Dabei ist zu vermuten, dass das reale Molekulargewicht auch etwa das Sechsfache des Wertes betragen kann, der aus dem nach der van Slyke'schen Methode ermittelten Aminostickstoffgehalt berechnet wurde.[21]

Wir beabsichtigen die einwandfreie Bestimmung des durchschnittlichen Molekulargewichtes auf anderen Wegen in der Kürze durchzuführen. Zur Zeit sind auch Versuche mit grösseren Ansätzen im Gange, deren erstes Ziel die Gewinnung von γ-Poly-glutaminsäuren viel höheren Molekulargewichtes und einer besseren Annäherung der Homodispersität ist.

Solange die Versuche mit grösseren Ansätzen nicht abgeschlossen sind, lässt sich auch keine endgültige Entscheidung darüber treffen, welche von den angeführten vier Methoden der Synthese als die zuverlässigste zu bezeichnen ist, da bei dieser Beurteilung die Grösse des Molekulargewichtes, die (auf die Startdipeptide berechnete) Ausbeute und die sichere Reproduzierbarkeit gemeinschaftlich in Rechenschaft gezogen werden müssen. Überdies, muss auch die optische Reinheit sämtlicher Endprodukte an grösseren Substanzproben nachgeprüft werden. Nach den bisherigen Versuchsergebnissen, die in Tabelle 2 zusammengefasst sind, scheint die erste Methode—bei Anwendung von Chlorameisensäure-i-propylester—die günstigste zu sein (Ausbeute 9,8% d.Th., auf das Startdipeptid berechnet; Aminostickstoff nach van Slyke 0,64%).

VERGLEICH DER STEREOISOMEREN γ-POLY-GLUTAMINSÄUREN MIT DEM APP BZW. SPP AUF SEROLOGISCHEM WEG

Herr Prof. Iványovics (Mikrobiologisches Institut der Universität Szeged) hat die synthetischen, stereoisomeren γ-Poly-glutaminsäuren der serologischen Prüfung unterworfen und in dieser Beziehung auch Polyglutaminsäuren anderen Typs untersucht,

[30] H. Sachs und E. Brand *J. Amer. Chem. Soc.* **76**, 3601 (1954).

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die ebenfalls in unserem Institut synthetisiert wurden. Über diese Untersuchungen berichtet Herr Prof. Ivánovics selbst ausführlich (s. im Anhang). Hier sei blos soviel hervorgehoben, dass mit Antianthrax-Immunseren Lösungen der γ-Poly-D-glutaminsäure—genau so wie Lösungen des APP's bzw. des SPP's—bis zu einer Verdünnung von 10^6 eine Präzipitationsreaktion zeigten, hingegen blieb diese Reaktion bei der γ-Poly-L-glutaminsäure aus. An Hand des serologischen Testes nach Ouchterlony[31] wurde zugleich die Polydispersität der synthetischen Produkte nachgewiesen.

Es ist somit festzustellen, dass sämtliche Eigenschaften der synthetischen γ-Poly-D-glutaminsäure mit denen des Anthrax-Polypeptids übereinstimmen. Auf Grunde dessen und der früheren Abbauergebnisse[7] kann man nun behaupten, dass das Anthrax-Polypeptid als γ-Poly-D-glutaminsäure (IIIb) anzusprechen ist. *Durch die Synthese dieser Polyglutaminsäure wurde erstmals die Vollsynthese eines natürlichen Haptens durchgeführt.*

Betreffs der Konstitution des Subtilis-Polypeptids ist es noch zu entscheiden, ob es sich hier um ein Gemisch von γ-Poly-D-glutaminsäure (IIIb) und γ-Poly-L-glutaminsäure (IIIa) handelt, oder ob Glutaminsäure-Bausteine entgegengesetzter Konfiguration in ein und derselben Polypeptidkette vergesellschaftet vorkommen. Nun zeigte nach Beobachtungen von Prof. Ivánovics auch die *mesoide* γ-Poly-glutaminsäure (IIIc) eine positive serologische Reaktion. Dadurch scheint auch die Möglichkeit, dass in den Peptidketten des SPP's D- und L-Glutaminsäure-Bausteine vergesellschaftet vorkommen, nicht a priori ausgeschlossen zu sein.

Es sei noch betont, dass nur die γ-Poly-D-glutaminsäure und die *mesoide* γ-Poly-glutaminsäure eine positive serologische Reaktion zeigte, während sich die bisher geprüften Poly-glutaminsäuren anderer Konstitution als serologisch inaktiv erwiesen.

BESCHREIBUNG DER VERSUCHE

Synthese der Startdipeptide (I) *und ihrer carboxylaktivierten Derivate*

(a) *Synthese des* L-L-*Startdipeptids* (Ia) *und seiner Derivate*

L-L-*Startdipeptid; γ-L-Glutamyl-L-glutaminsäure-αα'-dimethylester* (Ia). Die Synthese dieser Verbindung haben wir[12] und unabhängig von uns Waley[14] bereits beschrieben. Auf unterschiedliche Beobachtungen wurde im theoretischen Teil hingewiesen.

Carbobenzoxy-γ-L-glutamyl-L-glutaminsäure-αα'-dimethylester (XII; L-L-*Form*). S. unsere frühere Arbeit.[12] Schmp. 109–110°. $[\alpha]_D^{20} = -28{,}3$ ($c = 11{,}8$; Methanol).

Carbobenzoxy-γ-L-glutamyl-γ'-L-glutamylthiophenol-αα'-dimethylester (XVIII; L-L-*Form*). Eine mit Eis gekühlte und gerührte Lösung von 3,49 g des Carbobenzoxy-L-L-Startdipeptids (XII) in 20 ml absol. Tetrahydrofuran wurde zuerst mit 1,12 ml absol. Triäthylamin, dann binnen 15 Min. tropfenweise mit einem Gemisch von 0,77 ml Chlorameisensäureäthylester und 2 ml absol. Tetrahydrofuran versetzt. Nach weiteren 15 Min. versetzte man das Gemisch, das mit Kristallen des ausgeschiedenen Triäthylammoniumchlorids durchsetzt war, binnen 30 Min. tropfenweise mit einer Lösung von 0,87 ml Thiophenol in 3 ml absol. Tetrahydrofuran, rührte danach bei Raumtemperatur noch 1 Stunde weiter und liess zum Schluss das Gemisch 14 Stunden stehen. Nun wurde das Gemisch bei Unterdruck (Bad 25°) zur Trockne gebracht, der Rückstand auf dem Filter zuerst mit insgesamt 140 ml Wasser, dann nach dem

[31] Ö. Ouchterlony *Acta Path. Microbiol., Scand.* **26**, 507 (1949).

Trockensaugen mit 20 ml Petroläther gewaschen und schliesslich über Nacht im Vakuumexsiccator über P_2O_5 und Paraffin aufbewahrt. Dieses Rohprodukt (3,6 g) wurde zuerst aus 60 ml eines gleichteiligen Gemisches von Benzol und Petroläther umkristallisiert (Schmp. 124–126°). Nach einmaligem Umkristallisieren dieses Produktes wurden 2,73 g (64,6% d.Th.) einer analysenreinen Substanz vom Schmp. 134–135° gewonnen. $[\alpha]_{20}^{D} = -9{,}6°$ ($c = 4{,}0$; Tetrahydrofuran).

$C_{26}H_{36}O_8N_2S$ (530,6)

Ber.	C	58,85,	H	5,7,	N	5,3,	CH_3O 11,7
Gef.	C	59,0,	H	5,7,	N	5,7,	CH_3O 11,9

Hydrobromid des γ-L-Glutamyl-γ'-L-glutamyl-thiophenol-αα'-dimethylesters (XIX; L-L-*Form*). Man löste 3,5 g des reinen L-L-Thiophenylesters XVIII in 35 ml absol. Eisessig-Bromwasserstoff (10% HBr), liess die Lösung unter Feuchtigkeitsausschluss 1 Stunde stehen, versetzte sie danach unter Rühren mit 100 ml absol. Äther, wobei sich das Hydrobromid XIX als klebriges Produkt ausschied. Nach dem Abgiessen der Flüssigkeit wurde das Produkt dreimal mit je 100 ml absol. Äther durchgearbeitet, wodurch es zu einem Pulver zerfiel. Dieses wurde noch zweimal mit je 50 ml absol. Äther (Aufschlämmen, Abgiessen) gewaschen, dann im Vakuumexsiccator über Schwefelsäure getrocknet (3,0 g). Das Produkt ist sehr hygroskopisch. Kristallisationsversuche waren erfolglos.

(b) *Synthese des* D-D-*Startdipeptids* (I*b*) *und seiner Derivate*

Carbobenzoxy-D-glutaminsäure-γ-Hydrazid (IV; D-*Form*). Die Verbindung wurde auf dieselbe Weise hergestellt wie das entsprechende Derivat der L-Glutaminsäure.[12] Aus D-Glutaminsäure-hydrochlorid (52 g) wurde zuerst das Hydrochlorid des D-Glutaminsäure-γ-methylesters (30 g; Schmp. 156–158°; $[\alpha]_D^{20} = -24{,}2°$ ($c = 9{,}35$; Wasser), dann aus 28 g des Ester-hydrochlorids Carbobenzoxy-D-glutaminsäure-γ-methylester bereitet, der gleich im rohen Zustand mit Hydrazinhydrat umgesetzt wurde. Das zuerst anfallende, kristalline Carbobenzoxy-D-glutaminsäure-γ-hydrazid (27 g; 64% d.Th.) schmolz bei 168–169° (Zers.) und war zur weiteren Verarbeitung geeignet. Nach einmaligem Umkristallisieren aus wässrigen Alkohol (1 : 2) liess sich ein analysenreines Produkt gewinnen, das bei 177–178° schmolz. $[\alpha]_D^{20} = +11{,}5°$ ($c = 10{,}75$; *n*-Salzsäure).

$C_{13}H_{17}O_5N_3$ (295,3)

Ber.	C	52,9,	H	5,8,	N	14,2
Gef.	C	52,3,	H	5,85,	N	14,1

D-*Glutaminsäure-γ-benzylester* (VI; D-*Form*). Nach dem zur Herstellung des L-Stereoisomeren beschriebenen Verfahren[12] wurden aus 22 g D-Glutaminsäure 13,8 g (39% d.Th.) des aus Wasser einmal umkristallisierten D-Glutaminsäure-γ-benzylesters vom Schmp. 167–168° gewonnen, der zur weiteren Verarbeitung geeignet war. Nach wiederholtem Umkristallisieren aus Wasser blieb der Schmp. unverändert. $[\alpha]_D^{20} = -28{,}1°$ ($c = 9{,}8$, *n*-Salzsäure).

$C_{12}H_{15}O_4N$ (237,25)

Ber.	C	60,8,	H	6,3,	N	5,9
Gef.	C	60,65,	H	6,2,	N	6,1

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Carbobenzoxy-γ-D-glutamyl-D-glutaminsäure-γ'-benzylester (VII; D-D-*Form*). Aus 23,7 g Carbobenzoxy-D-glutaminsäure-γ-hydrazid (IV) vom Schmp. 168–169° und 18,9 g D-Glutaminsäure-γ-benzylester (VI) auf analoge Weise bereitet wie das stereoisomere L-L-Produkt.[12] Ausbeute an unmittelbar anfallenden kristallinen Produkt 21,4 g (61% d.Th., nach Abrechnung des unverändert gebliebenen Benzylesters, 2,2 g). Schmp: Ziehend 153–159°, nach vorherigem Sintern bei 138°. Obzwar das Produkt mit der strukturisomeren Verbindung IX verunreinigt ist (s. im allgem. Teil und a.a.O.[12]) wurde es weiter verarbeitet. Zur Analyse wurde eine Probe (2 g) aus Alkohol (10 ml) einmal umkristallisisert. Schmp. 160–162°, nach vorherigem Sintern bei 156°. $[\alpha]_D^{20} = +6{,}7°$ ($c = 4{,}7$; Methanol).

$C_{25}H_{28}O_9N_2$ (500,5)

Ber.	C 60,0,	H 5,6,	N 5,6		
Gef.	C 59,6,	H 5,7,	N 5,6		

Carbobenzoxy-γ-D-glutamyl-D-glutaminsäure-αα'-dimethyl-γ'-benzyl-ester (VIII; D-D-*Form*). Aus 7 g Carbobenzoxy-γ-D-glutamyl-D-glutaminsäure-γ-benzylester (VII) vom Schmp. 153–159° (s. oben) wurden nach dem bei der Herstellung der L-L-Form angewandten Verfahren[12] 5 g (67,7% d.Th.) der Substanz VIII vom Schmp. 116–117° gewonnen; sie wurde weiter verarbeitet. Zur Analyse wurde eine kleine Probe aus Methanol einmal umkristallisiert. Schmp. 119–120°. $[\alpha]_D^{20} = +7{,}3°$ ($c = 4{,}9$; Essigester).

$C_{27}H_{32}O_9N_2$ (528,5)

Ber.	C 61,35,	H 6,1,	CH_3O 11,7		
Gef.	C 61,7,	H 6,1,	CH_3O 11,8		

Die frühere Angabe[12] über den spez. Drehwert des L-L-Antipoden ist nach den jetzt durchgeführten Kontrollbestimmungen auf $[\alpha]_D^{20} = -7{,}1°$ ($c = 5{,}5$; Essigester) zu korrigieren.

D-D-*Startdipeptid; γ-D-Glutamyl-D-glutaminsäure-αα'-dimethylester* (Ib). Aus 8 g des obigen Produktes (VIII) vom Schmp. 116–117° wurden nach dem für die Herstellung des L-L-Startdipeptids (Ia) beschriebenen Verfahren[12] 3,1 g (64% d.Th.) des D-D-Startdipeptids (Ib) gewonnen. Das unmittelbar anfallende, mit Methanol–Äther, danach mit Äther gewaschene Kristallprodukt schmolz rasch erhitzt nach vorherigem Sintern bei 129–130°. Das so gewonnene Produkt enthält 1 Mol. Kristallwasser. $[\alpha]_D^{20} = +3{,}3°$ ($c = 4{,}86$; Methanol). Die frühere Angabe[12] über den spez. Drehwert des L-L-Antipoden ist nach den jetzt durchgeführten Kontrollbestimmungen auf $[\alpha]_D^{20} = -3{,}2°$ ($c = 4{,}72$; Methanol) zu korrigieren.

$C_{12}H_{20}O_7N_2, H_2O$ (322,3)

Ber.	C 44,7,	H 6,9,	N 8,7	CH_3O 19,25	
Gef.	C 45,2,	H 6,75,	N 8,6	CH_3O 19,2	

Prüfung der Einheitlichkeit der Verbindungen VII *und* VIII (D-D-*Form*), *weiterhin des* D-D-*Startdipeptids* (Ib). Je 0,3 g des Produktes VII (D-D-Form) vom Schmp. 160–162° und seines methylierten Derivates (VIII; D-D-Form) vom Schmp. 119–120° wurden

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in 80 prozent. Essigsäure (25 ml) hydrogenolysiert (Pd-Tierkohle, 10% Pd), das Filtrat bei Unterdruck eingedampft und die beiden Rückstände, weiterhin 0,3 g des D-D-Startdipeptids (Ib) vom Schmp. 129–130° in je 50 ml Wasser gelöst. Je 0,01 ml dieser Lösungen wurden chromatographiert. Lösungsmittel: Eisessig–*n*-Butanol–Wasser 1 : 4 : 5; aufsteigende Chromatographie auf Macherey-Nagel Nr. 518-Papier; Entwicklung mit Ninhydrin. Substanz VII lieferte zwei etwas zusammengeschmolzene, durch ihre verschiedene Intensität unterscheidbare Flecke, $R_f = 0{,}21$–$0{,}24$, die auf die Anwesenheit von γ-D-Glutamyl-D-glutaminsäure und α-D-Glutamyl-D-glutaminsäure hindeuten. Substanz VIII lieferte einen sehr intensiv angefärbten Fleck des γ-D-Glutamyl-D-glutaminsäure-αα′-dimethylesters ($R_f = 0{,}50$), weiterhin einem viel kleineren und nur ganz schwach angefärbten Fleck des α-D-Glutamyl-D-glutaminsäure-γα′-dimethylesters ($R_f = 0{,}34$). Bei Substanz Ib ist der Fleck $R_f = 0{,}50$ sehr intensiv angefärbt, während der bedeutend kleinere Fleck $R_f = 0{,}34$ eben nur die Empfindlichkeitsgrenze (etwa 0,2 γ) der Ninhydrinreaktion des α-D-Glutamyl-D-glutaminsäure-γα′-dimethylesters (XI) erreicht. Daraus folgt, dass diese Verunreinigung im D-D-Startdipeptid (Ib) vom Schmp. 129–130° unter 0,5% liegt.

Carbobenzoxy-γ-D-glutamyl-D-glutaminsäure-αα′-dimethylester (XII; D-D-*Form*). Nach dem für die Carbobenzoxylierung des L-L-Startdipeptids angewandten Verfahren[12] wurden aus 2,65 g des D-D-Startdipeptids (Ib) 1,68 g (47% d.Th.) seines Carbobenzoxy-Derivats (XII) in analysenreinem Zustand gewonnen. Schmp. 109–110°. $[\alpha]_D^{20} = +28{,}3°$ ($c = 9{,}8$; Methanol).

Carbobenzoxy-γ-D-glutamyl-γ′-D-glutamyl-thiophenol-αα′-dimethylester (XVIII; D-D-*Form*). Nach der Herstellungsart der stereoisomeren L-L-Verbindung (XVIII; L-L-Form) wurden aus 1,54 g des Carbobenzoxy-D-D-Startdipeptids 1,15 g (61,7% d.Th.) der D-D-Verbindung (XVIII) in analysenreinem Zustand gewonnen. Schmp. 133–135°.

Hydrobromid des γ-D-Glutamyl-γ′-D-glutamyl-thiophenol-αα′-dimethylesters (XIX; D-D-Form). Aus 1,1 g des D-D-Thiophenylesters XVIII wurde nach der Herstellungsart des Hydrobromids XIX der L-L-Form das rohe D-D-Hydrobromid (XIX) in Form eines hygroskopischen Pulvers in fast quantitativer Ausbeute gewonnen.

(c) *Synthese des* L-D-*Startdipeptids und seiner Derivate*

Sämtliche Schritte sind der Synthese des L-L-Startdipeptids bzw. D-D-Startdipeptids und seiner Derivate nachgebildet worden. Nachstehend wurden nur die Ansätze, Ausbeuten, die Art der Kristallisation, die Analysendaten und die physikalischen Konstanten angegeben.

Carbobenzoxy-γ-L-glutamyl-D-glutaminsäure-γ′-benzylester (VII; L-D-Form). Aus 11,8 g IV (L-Form) und 7,7 g VI (D-Form) 8 g (47% d.Th.) des Rohproduktes. Einmal umkristallisiert aus 180 ml Essigester–Äther (1 : 1) 5,24 g, aus der Mutterlauge weitere 2,2 g Schmp. 135–137°. Aus Essigester noch einmal umkristallisiert: Schmp. 137–138°. $[\alpha]_D^{20} = -1{,}12°$ ($c = 8{,}9$; Methanol).

$C_{25}H_{28}O_9N_2$ (500,5)

Ber.	C	60,0,	H	5,6,	N	5,6
Gef.	C	60,1,	H	5,5,	N	5,3

Carbobenzoxy-γ-L-glutamyl-D-glutaminsäure-αα′-dimethyl-γ′-benzyl-ester (VIII; L-D-*Form*). Aus 7,4 g VII (L-D-Form) 4,1 g (52% d.Th.) VIII (L-D-Form) vom Schmp.

104–107°. Aus absol. Essigester (12 ml) umkristallisiert 3,15 g vom Schmp. 107–108,5°. $[\alpha]_D^{20} = +0{,}95°$ ($c = 11{,}5$; Aceton).

$C_{27}H_{32}O_9N_2$ (528,5)

Ber.	C	61,35,	H	6,1,	N	5,3,	CH_3O 11,7
Gef.	C	61,6,	H	6,3,	N	5,3,	CH_3O 12,0

L-D-*Startdipeptid: γ-L-Glutamyl-D-glutaminsäure-αα'-dimethylester* (Ic). Aus 3,1 g VIII (L-D-Form) 1,2 g (66% d.Th.) des aus Methanol (7 ml) einmal umkristallisierten L-D-Startdipeptids. Schmp. 143–144°. $[\alpha]_D^{20} = +38{,}6°$ ($c = 5{,}5$; Methanol).

$C_{12}H_{20}O_7N_2$ (304,3)

Ber.	N	9,2,	CH_3O	20,4
Gef.	N	9,4,	CH_3O	20,3

Die chromatographische Prüfung der Einheitlichkeit des Produktes erfolgte ebenso wie beim D-D-Startdipeptid und brachte dasselbe Ergebnis.

Carbobenzoxy-γ-L-glutamyl-D-glutaminsäure-αα'-dimethylester (XII; L-D-*Form*). Aus 1 g L-D-Startdipeptid (Ic) 0,5 g (35% d.Th.) des kristallinen Rohproduktes; aus 4 ml absol. Essigester–Äther (1 : 1) zweimal umkristallisiert 0,35 g vom Schmp. 136–137°. $[\alpha]_D^{20} = +4{,}3°$ ($c = 8{,}2$; Methanol).

$C_{20}H_{26}O_9N_2$ (438,4)

Ber.	C	54,8,	H	6,0,	N	6,4
Gef.	C	55,0,	H	6,1,	N	6,7.

Carbobenzoxy-γ-L-glutamyl-γ'-D-glutamyl-thiophenol-αα'-dimethylester (XVIII; L-D-*Form*). Aus 3 g des Carbobenzoxy-L-D-Startdipeptids (XII; L-D-Form) fiel nach der Herstellungsart der stereoisomeren L-L-Verbindung (XVIII; L-L-Form) zuerst ein mit Kristallen durchsetztes Öl an. Dieses wurde in Essigester gelöst, die Lösung zuerst zwecks Entfernung des Triäthylammoniumchlorids mit Wasser ausgeschüttelt, dann getrocknet (Na_2SO_4) und schliesslich bei Unterdruck eingedampft. Der so gewonnene ölige Rückstand kristallisierte allmählich beim Verreiben mit absol. Äther. Das Kristallprodukt wurde zuerst aus absol. Methanol–Äther (1 : 4), dann aus absol. Methanol je einmal umkristallisiert. Das Produkt (0,65 g; 17,9% d.Th.) schmolz unscharf bei 97–100° nach vorherigem Sintern bei 94°. Wegen Materialmangels wurde auf eine weitere Reinigung verzichtet.

Hydrobromid des γ-L-Glutamyl-γ'-D-glutamylthiophenol-αα'-dimethylesters (XIX; L-D-*Form*). Aus 0,62 g des L-D-Thiophenylesters XVIII wurde nach der Herstellungsart des Hydrobromids XIX der L-L-Form das rohe L-D-Hydrobromid (XIX) in Form eines hygroskopischen Pulvers in nahezu quantitativer Ausbeute gewonnen.

Umsetzung der stereoisomeren Startdipeptide (I) *bzw. ihrer Derivate zum γ-Polyglutaminsäure-α-methylester entsprechender Konfiguration*

Erste Methode

(a) *Herstellung des* L-*Polyesters* (IIa, *bzw.* XVI) *aus dem Carbobenzoxy-*L-L-*Startdipeptid* (XII; L-L-*Form*). In einem Zweihalskölbchen wurde eine Lösung von

1,46 g Carbobenzoxy-γ-L-glutamyl-L-glutaminsäure-αα′-dimethylester(XI I; L-L-Form) in 3 ml reinstem, wasserfreiem Dimethylformamid unter Feuchtigkeitsausschluss, nebst Eiskühlung und Rühren zuerst mit 0,47 ml absol. Triäthylamin, dann tropfenweise mit einem Gemisch von 0,32 ml Chlorameisensäureäthylester und 2 ml Dimethylformamid versetzt. Man rührte noch 10 Min. weiter, versetzte danach das Gemisch—das mit den Kristallen des ausgeschiedenen Triäthylammoniumchlorids durchsetzt war—mit 0,5 g Pd-Tierkohle (10% Pd), verband den einen Hals mit einem bis zum Boden des Kölbchens reichenden Gaseinleitungsrohr, den anderen durch eine vorgeschaltete, mit konz. Schwefelsäure beschickte Waschflasche mit einem abgewogenen Geissler'schen Kaliapparat. Jetzt liess man durch das Gemisch unter ständiger Eiskühlung einen langsamen Wasserstoffstrom (1 Blase per Sec.) streichen. Durch zeitweisiges Unterbrechen der Wasserstoffzufuhr und Abwägen des Kaliapparates konnte man feststellen, dass binnen 5 Stunden rund 1 Mol. (0,15 g) CO_2 abgegeben worden war. Da jedoch die CO_2-Abgabe bei diesem Stadium noch nicht zum Stillstand kam, wurde der Versuch weiter geleitet. Nach weiteren 2½ Stunden war die CO_2-Abgabe praktisch beendet und betrug insgesamt 1,36 Mol. (0,20 g). Jetzt wurde das Gemisch abgeschleudert, der Bodensatz einmal mit 3 ml Dimethylformamid durch Aufschlämmen und Abschleudern ausgewaschen, die vereinigte Lösung nach Zusatz von 0,47 ml Triäthylamin 3 Stunden bei Raumtemperatur stehen gelassen, dann eine Stunde auf 60° erwärmt und schliesslich i. Vak. (20 mm) eingedampft (Bad 80°), wobei ein zähflüssiges, braunes Öl zurückblieb. Dieses wurde 8 mal mit je 40 ml absol. Äther gründlich zerrieben, dann im Vakuumexsiccator über Schwefelsäure aufbewahrt. Das so gewonnene, pulverisierbare Produkt, das vom anhaftenden Katalysator graustichig war, wog 177 mg (18,6% d.Th. auf das Carbobenzoxy-L-L-Startdipeptid, etwa 9,3% d.Th. auf das L-L-Startdipeptid berechnet). Das Rohprodukt (Polyester I-a) wurde ohne Reinigung weiter verarbeitet.

(b) *Herstellung des* L-*Polyesters* (IIa) *unmittelbar aus dem* L-L-*Startdipeptid* (Ia). *Mittels Chlorameisensäureäthylester.* Eine Lösung von 2,0 g des L-L-Startdipeptids (Ia) in 11 ml Dimethylformamid wurde nebst Rühren und Kühlung (—4°) zuerst mit 0,87 ml Triäthylamin, dann tropfenweise mit einem Gemisch von 0,53 ml Chlorameisensäureäthylester und 3 ml Dimethylformamid versetzt. Man rührte noch 15 Min. weiter, nutschte dann das ausgeschiedene Triäthylammoniumchlorid rasch ab, wusch es zweimal mit je 2 ml Dimethylformamid nach und engte das mit der Waschflüssigkeit vereinigte Filtrat im Hochvakuum (Bad 0°) bis auf etwa 4 ml ein. Diese Lösung wurde nach Zusatz von 0,87 ml Triäthylamin 8 Stunden auf 40–60° erwärmt, dann über Nacht stehen gelassen, wobei eine geringe Kristallausscheidung erfolgte. Deren unbeachtet wurde das Gemisch i. Vak. (Bad 80°) ganz eingedampft, der Rückstand in 5 ml Methanol gelöst, die Lösung bei Unterdruck abermals abgedampft, und diese Prozedur noch einmal wiederholt. Das so gewonnene rötlichbraune, zähflüssige Öl (2,7 g) wurde in 15 ml Wasser gelöst, die Lösung gegen insgesamt 2 l. dest Wasser (in vier Ansätzen) 46 Stunden dialysiert (Cellophan), dann der Gefriertrocknung unterworfen und der feste Polyester 24 Stunden im Vakuumexsiccator über P_2O_5 aufbewahrt. Das sandfarbige, amorphe Produkt (Polyester I-b) wog 688 mg (38,8% d.Th.); es wurde ohne Reinigung weiter verarbeitet.

$[C_6H_9O_3N]_n$ $[143.14]_n$

Ber.	CH_3O	21,7
Gef.	CH_3O	22,0

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Mittels Chlorameisensäure-i-propylester. Eine Lösung von 2,0 g des L-L-Startdipeptids in 12 ml absol. Dimethylformamid wurde nach Zusatz von 3 ml absol. Toluol i. Vak. (8 mm; Bad 50°) bis auf etwa 6 ml eingeengt, dann die teilweise ausgeschiedene Substanz durch Zusatz von 6 ml Dimethylformamid durch gelindes Erwärmen wieder gelöst. Man versetzte die Lösung zuerst mit 0,87 ml Triäthylamin, hierauf—nebst starker Kühlung (Bad —10°)—tropfenweise und unter Rühren mit einem Gemisch von 0,72 ml Chlorameisensäure-*i*-propylester und 2 ml Dimethylformamid. Es wurde noch weitere 20 Min. unter Kühlung gerührt, dann Triäthylamin (0,87 ml) zugesetzt und nachher allmählich auf Raumtemperatur gebracht. Nun wurde die mit Kristallen (Triäthylammoniumchlorid) durchsetzte Lösung 3 Stunden auf 50°, dann 1 Stunde auf 70° erwärmt und nachher i. Vak. (10 mm) eingedampft. Der Rückstand wurde mit 30 ml absol. Äther verrieben und das Gemisch über Nacht im Eisschrank stehen gelassen. Nach Abgiessen des Äthers wurde das zähflüssige, mit Kristallen durchsetzte Produkt in 20 ml Methanol aufgenommen, das Gemisch bei Unterdruck scharf abgedampft und diese Prozedur noch einmal wiederholt. Der Rückstand wurde in 25 ml dest. Wasser gelöst, die Lösung zuerst gegen 3½ l. dest. Wasser (in vier Ansätzen) 72 Stunden dialysiert (Cellophan), dann der Gefriertrocknung unterworfen. Das sandfarbige, amorphe Produkt (Polyester 1-b′) wog 773 mg (43,5% d.Th.).

$[C_6H_9O_3N]_n$ [143,14]$_n$

Ber.	CH_3O	21,7
Gef.	CH_3O	21,0

Zweite Methode

γ-Poly-L-glutaminsäure-α-methylester (IIa, bzw. XXI). Eine Lösung von 3 g des rohen Hydrobromids XIX (L-L-Form) in 3 ml absol. Aceton wurde nach Zusatz von 1,8 ml absol. Triäthylamin nebst Feuchtigkeitsausschluss 24 Stunden sich selbst überlassen. Ungeachtet der kristallinen Ausscheidung (Triäthylammoniumbromid) wurde aus dem Gemisch mit Hilfe eines Heizbades (100°) der grösste Teil der Flüssigkeit abdestilliert, dann der ölige Rückstand unter Feuchtigkeitsausschluss 3 Stunden auf 100° erwärmt. Nach dem Abkühlen wurde der zähflüssige Rückstand mit 150 ml absol. Äther übergossen und 12 Stunden im Eisschrank stehen gelassen. Während dessen erhärtete sich das Produkt derart, dass es sich (unter Äther) zu einem feinen Pulver zerreiben liess. Dieses wurde abgeschleudert, dann in der Zentrifuge der Reihe nach dreimal mit je 70 ml Äther, dreimal mit je 30 ml Wasser, dreimal mit je 50 ml Aceton und schliesslich zweimal mit je 50 ml absol. Äther gewaschen. Das so gewonnene, fast farblose Produkt (L-Polyester 2) wurde zuerst an der Luft, dann im Vakuumexsiccator über P_2O_5 getrocknet. Ausbeute 400 mg (21,2% d.Th. auf den carbobenzoxylierten Thiophenylester XVIII, etwa 6,8% d.Th. auf das L-L-Startdipeptid berechnet).

$[C_6H_9O_3N]_n$ [143,14]$_n$

Ber.	C	50,4,	H	6,3,	N	9,8,	CH_3O 21,7
Gef.	C	49,6,	H	5,7,	N	9,6,	CH_3O 21,9

γ-Poly-D-glutaminsäure-α-methylester (IIb, bzw. XXI). Aus 1,1 g Carbobenzoxy-γ-D-glutamyl-γ′-D-glutamylthiophenol-αα′-dimethylester (XVIII; D-D-Form) gewonnenes, rohes Hydrobromid XIX (D-D-Form) wurde auf die oben angegebene Weise

umgesetzt. Das gewonnene Produkt (D-Polyester 2) wog 139 mg (23,4% d.Th. auf den carbobenzoxylierten Thiophenylester XVIII, etwa 7,2% auf das D-D-Startdipeptid berechnet).

mesoider *γ-Poly-glutaminsäure-α-methylester* (IIc, bzw. XXI). Aus 620 mg Carbobenzoxy-γ-L-glutamyl-γ′-D-glutamylthiophenol-αα′-dimethylester (XVIII) gewonnenes, rohes Hydrobromid XIX (L-D-Form) wurde auf die oben angegebene Weise umgesetzt. Das gewonnene Produkt (L-D-Polyester 2) wog 220 mg (65,8% d.Th. auf den carbobenzoxylierten Thiophenylester XVIII, 4,1% d.Th. auf das L-D-Startdipeptid berechnet.)

Dritte Methode

γ-Poly-L-glutaminsäure-α-methylester (IIa). In einer Lösung von 3,2 g (0,1 Mol.) des L-L-Startdipeptids (Ia) in 6,5 ml Dimethylformamid wurden 2,3 g (0,11 Mol.) frisch destillierten Di*cyclo*hexylcarbodiimids gelöst. Es erfolgte eine starke Selbsterwärmung und nach etwa 10 Min. setzte die Ausscheidung von Di*cyclo*hexylharnstoff ein. Man erwärmte das Reaktionsgemisch unter Feuchtigkeitsausschluss 4 Stunden am siedenden Wasserbad, kühlte danach ab, nutschte den Di*cyclo*hexylharnstoff (1,7 g) ab, und wusch ihn am Filter mit eiskaltem Dimethylformamid nach. Das vereinigte Filtrat wurde bei Unterdruck (20 mm; Bad 90°) eingedampft, der zähflüssige Rückstand mit insgesamt 200 ml absol. Äther wiederholt solange digeriert bis er zu einem Pulver zerfiel. Das so gewonnene Produkt (2,4 g) stellt ein Gemisch des amorphen Polyesters (L-Polyester 3) und kristallinen Di*cyclo*hexylharnstoffs (ber. zurückgebliebene Menge 0,8 g) dar. Ausbeute an Polyester etwa 1,6 g (56,3% d.Th.). Da das Harnstoffderivat nicht vollständig entfernt werden konnte, wurde das Mischprodukt unmittelbar zur Herstellung der γ-Poly-L-glutaminsäure herangezogen.

γ-Poly-D-glutaminsäure-α-methylester (IIb). Aus 1,35 g des D-D-Startdipeptids (Ib) wurden auf den oben angegebenen Weg 1,3 g eines pulverartigen Produktes gewonnen, das ein Gemisch des amorphen Polyesters (D-Polyester 3) und kristallinen Di*cyclo*hexylharnstoffs (etwa 0,5 g) darstellt. Ausbeute an Polyester etwa 0,8 g (66,7% d.Th.). Das Produkt wurde unmittelbar zur Herstellung der γ-Poly-D-glutaminsäure herangezogen.

Vierte Methode

γ-Poly-L-glutaminsäure-α-methylester (IIa). Eine mit Eis gekühlte Suspension von 3,22 g (0,01 Mol.) des L-L-Startdipeptids (Ia) in 15 ml absol. Chloroform wurde zuerst mit 1,39 ml (0,01 Mol.) Triäthylamin, dann tropfenweise unter Schütteln mit 1,45 ml (0,01 Mol.) Chlorameisensäurethiophenylester versetzt. Unter gelinder Selbsterwärmung ging ein erheblicher Teil der umgesetzten Substanz sofort in Lösung. Das Gemisch wurde in geschlossenen Gefäss 4 Stunden auf der Maschine geschüttelt, dann das unumgesetzte Startdipeptid (0,55 g) abfiltriert, das Filtrat zweimal mit Wasser, einmal mit verd. Salzsäure, zweimal wiederum mit Wasser ausgeschüttelt, hierauf mit Na_2SO_4 getrocknet und zum Schluss bei Unterdruck und Raumtemperatur eingedampft. Es blieb ein gelbliches, zähflüssiges Öl zurück, das durch wiederholtes Verreiben mit absol. Äther zu einem Pulver zerfiel. Dieses "primäre Umsetzungsprodukt", das 1,3 g wog, konnte nicht kristallisiert werden. Es wurde unmittelbar zum Polyester umgesetzt.

Das "Primäre Umsetzungsprodukt" (1,3 g) wurde in einem Gemisch von 4 ml absol.

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Pyridin und 16 ml absol. Benzol gelöst. Schon nach einigen Minuten erschien eine schwache Trübung. Das Gemisch wurde unter Feuchtigkeitsausschluss in einem 90° warmen Bad erwärmt, wobei die Substanzausscheidung fortschritt und die Hauptmenge des Produktes sich filmartig an die Kolbenwand ansetzte; die Lösung bekam eine schmutziggelbe Farbe. Nach etwa 60 Stunden war die Ausscheidung des Produktes praktisch beendet. Die Substanz wurde in der Zentrifuge abgetrennt, dann mehrere Mal mit absol. Aceton und hierauf mit absol. Äther gewaschen, schliesslich im Vakuumexsiccator über Schwefelsäure getrocknet. Der so gewonnene Polyester (L-Polyester 4) stellt ein schwach sandfarbiges, amorphes Pulver dar. Ausbeute 610 mg (25,7% d.Th. auf das L-L-Startdipeptid berechnet, abgerechnet den nicht umgesetzten Anteil). Zur Analyse wurde eine Probe in Methanol gelöst, mit Äther ausgefällt, abgeschleudert, dann in der Vakuumpisole über P_2O_5 zuerst bei Raumtemperatur und schliesslich bei 78° getrocknet.

$[C_6H_9O_3N]_n$ [143,14]$_n$

Ber.	C	50,4,	H	6,3,	N	9,8,	CH_3O 21,7
Gef.	C	49,5,	H	6,1,	N	9,9,	CH_3O 21,0

Konstitutionsermittelnder Abbau des γ-Poly-L-glutaminsäure-α-methylesters. 100 mg des nach der zweiten Methode gewonnenen Polyesters (L-Polyester 2) wurden mit 10 ml flüssigem Ammoniak im Bombenrohr 72 Stunden bei Raumtemperatur stehen gelassen. Während dessen ging die Substanz fast ganz in Lösung. Nachdem sich das Ammoniak aus dem geöffneten Rohr verflüchtigt hatte, wurde der feste Rückstand im Zentrifugenrohr zweimal mit je 50 ml Wasser, dann zweimal mit je 50 ml eines gleichteiligen Gemisches von Alkohol und Äther, und schliesslich dreimal mit je 30 ml absol. Äther gewaschen. Das an der Luft, danach im Vakuumexsiccator über P_2O_5 getrocknete, weisse, amorphe Polyamid (IIa; R = NH_2 anstatt OCH_3) wog 62 mg (69,3% d.Th.). Zur Analyse wurde eine kleine Probe noch 5 Stunden in der Pistole über P_2O_5 bei 80° getrocknet.

$[C_5H_8O_2N_2]_n$ [128,14]$_n$

Ber.	N	21,8	
Gef.	N	20,6	

Es sei erwähnt dass das Polyamid, das aus dem SPP über den Methylester auf dieselbe Weise hergestellt worden ist, genau denselben Stickstoffgehalt (20,6%) aufwies.[32]

50 mg des Polyamids wurden mit 0,98 ml einer 2,68 proz. alkalischen Natriumhypochloritlösung unter häufigem Umschwenken zuerst 1 Stunde bei Raumtemperatur, dann 15 Min. bei 60° behandelt, wobei die Substanz fast ganz in Lösung ging. Nach Zusatz von 10 ml 6 *n*-Salzsäure wurde die Lösung 30 Min. rückfliessend gekocht und dann bei Unterdruck trocken gedampft. Der Rückstand wurde noch zweimal in je 2 ml Wasser gelöst und die Lösung bei Unterdruck eingedampft. Den so gewonnenen Rückstand versetzte man mit 1 ml einer frisch bereiteten, bei Raumtempetatur gesättigten Lösung von *p*-Nitrophenylhydrazin in *n*-Salzsäure, tauchte das Gemisch einige Sek. in ein 70° warmes Bad und liess es danach 15 Min. unter Eiskühlung stehen. Das kristallin ausgeschiedene *β-Formylpropionsäure*-p-*nitrophenylhydrazon* wurde abgenutscht, auf dem Filter zweimal mit je 1 ml eiskaltem

[32] V. Bruckner, J. Kovács und H. Nagy *J. Chem. Soc.* 148 (1953).

Wasser gewaschen und schliesslich im Vakuumexsiccator getrocknet. Es wog 20 mg und schmolz bei 172°. Nach einmaligem Umkristallisieren aus 1 ml Wasser wurde ein analysenreines Produkt gewonnen, das übereinstimmend mit der Literaturangabe[33] bei 177° schmolz und in der Mischprobe mit einem authentischen Präparat vom Schmp. 177° keine Depression zeigte.

30 mg des Polyamids wurden auf oben angegebene Art mit Natriumhypochlorit behandelt, dann die Lösung mit Wasser auf 4 ml verdünnt. Die eine Hälfte dieser Lösung wurde unmittelbar, die andere (Kontrollversuch) nach Zusatz von 0,7 mg αγ-Diaminobuttersäure zum Nachweis der für die α-Glutamylbindung charakteristischen[8, 10] αγ-Diaminobuttersäure herangezogen. Man versetzte jede Lösung mit 2 ml rauchender Salzsäure und kochte sie danach 2 Stunden rückfliessend. Die abgekühlte Lösung wurde—zwecks Entfernung der β-Formylpropionsäure—24 Stunden im Apparat mit Äther ausgezogen, dann bei Unterdruck trocken gedampft, der Rückstand mit 5 ml eiskalter, rauchender Salzsäure versetzt, das ausgeschiedene NaCl abfiltriert und das Filtrat bei Unterdruck trocken gedampft. Diese Behandlung des Rückstandes mit rauchender Salzsäure wurde so lange wiederholt, bis eine Ausscheidung von NaCl nicht mehr erfolgte. Die zum Schluss gewonnenen Rückstände der beiden Proben wurden in je 1 ml Wasser gelöst und je 0,01 ml dieser Lösungen der Papierchromatographie unterworfen. (Aufsteigende Chromatographie auf Wh. No. 4 Papier; Lösungsmittel *n*-Butanol–Eisessig–Wasser 4 : 1 : 5; Entwicklung mit Ninhydrin.) Während im Kontrollversuch ausser dem Fleck der Glutaminsäure auch der Fleck der αγ-Diaminobuttersäure ganz deutlich erscheint, fehlt der letztere beim originalen Ansatz.

Herstellung der γ-Poly-glutaminsäuren (III) *verschiedener Konfiguration aus den entsprechenden Polyestern*

Ansätze von 100–1600 mg der verschiedenen Polyester wurden mit einem 50–100-proz. Überschuss von 0,25 *n*-NaOH 1 Stunden am Dampfbad erhitzt, die Lösung nötigenfalles (z.B. bei der Verarbeitung des nach der vierten Methode gewonnenen Polyesters zwecks Entfernung des unlöslich gebliebenen Di*cyclo*hexylharnstoffs) abfiltriert, dann bei p_H 6 (Einstellung mit Salzsäure, bzw. mit Natronlauge) mit einer gesättigten Kupfer(II)sulfat-Lösung das Kupfersalz der Polysäure ausgefällt. Letzteres wurde abgeschleudert und in der Zentrifuge 3-4-mal mit wenig eiskaltem Wasser gewaschen. Man löste den feuchten Niederschlag in der eben zureichenden Menge von 0,1 *n*-HCl auf; diese Menge betrug der Regel nach 1 ml je 10–15 mg des angesetzten Polyesters. Diese Lösung wurde mit Schwefelwasserstoff gesättigt, dann der Überschuss des letzteren mit einem Luftstrom entfernt, der Niederschlag abgeschleudert, in der Zentrifuge 2-mal mit wenig Wasser gewaschen, die mit dem Waschwasser vereinigte Lösung nötigenfalles klarfiltriert, dann gegen dest. Wasser der Dialyse unterworfen unter Verwendung einer Cellophanmembrane (Dialysierschlauch). Die Dialyse wurde bis zum Verschwinden der Chloridreaktion vorgenommen; die Gesamtmenge des 8–12 mal gewechselten Aussenwassers betrug in der Regel 12–15 ml auf je 1 mg des angesetzten Polyesters. Die zurückgebliebene Lösung wurde i. Vak. (Bad 30°) auf 10–20 ml eingeengt, dann der Gefriertrocknung unterworfen. In kolloidaler Form etwa mitgeschlepptes Kupfer(II)sulfid koaguliert im Laufe der Gefriertrocknung und lässt sich durch Lösen des Rückstandes in Wasser,

[33] C. Harries *Ber. Dtsch. Chem. Ges.* **45**, 2585 (1912).

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Abfiltrieren der Lösung und Gefriertrocknung des Filtrats vollkommen entfernen.

Die so gewonnene γ-Poly-glutaminsäuren stellen schneeweisse, flaumartige Produkte dar, die in Wasser sehr leicht löslich sind. Sie zeigen—in Übereinstimmung mit dem APP und SPP—keine Biuretreaktion, ihre Ninhydrinreaktion ist—im Vergleich mit der γ-L-Glutamyl-L-glutaminsäure—nur schwach positiv; während die Empfindlichkeitsgrenze der Reaktion (auf Papier getestet) bei der letzteren Substanz etwa 0,2 γ beträgt, liegt sie bei den synthetischen γ-Poly-glutaminsäuren bei etwa 10 γ, stieg jedoch fallweise bis 20 γ an. Beim SPP ursprünglicher Darstellungsart[1] liegt die Empfindlichkeitsgrenze zu mindest bei 25 γ. In Tabelle 1 sind einige Versuchsdaten zusammengefasst; hierzu ist zu bemerken, dass die Ausbeuten nicht auf den angesetzten

Tabelle 1

Hergestelltes Produkt	Angesetzter Polyester		Gewonnene γ-Poly-Glu.		
	Herstellungsart	Menge (mg)	Menge (mg)	H_2N-N (%)	Ausbeute (%)
(1) γ-Poly-L-Glu.	L-Polyester 1-a	176	48		1,1
(2) γ-Poly-L-Glu.	L-Polyester 1-b	688	89	1,18	7,1
(3) γ-Poly-L-Glu.	L-Polyester 1-b'	762	138	0,61	9,8
(4) γ-Poly-L-Glu.	L-Polyester 2	100	44	1,50	3,9
(5) γ-Poly-L-Glu.	L-Polyester 3	~1600	142	0,49	6,3
(6) γ-Poly-L-Glu.	L-Polyester 4	252	73	0,32	7,8
(7) γ-Poly-D-Glu.	D-Polyester 2	138	86	1,50 (0,82)*	5,4 (4,4)*
(8) γ-Poly-D-Glu.	D-Polyester 3	~900	60	0,16	6,3
(9) *meso*-γ-Poly-Glu.	L-D-Polyester 2	220	70	3,6 (2,9)†	1,3

* Produkt (7) wiederholt dialysiert.
† Produkt (9) wiederholt dialysiert.

Polyester, sondern auf das entsprechende Startdipeptid berechnet wurden, und zwar auch dann, wenn der Polykondensation nicht unmittelbar das Startdipeptid, sondern sein Derivat herangezogen wurde.

All die in Tabelle 1 angeführten γ-Poly-glutaminsäuren weisen eine erhebliche Polydispersität auf. Dies liess sich nicht nur bei den serologisch aktiven Polysäuren an Hand der Testungsmethode nach Ouchterlony[31] zeigen (s. die nachstehende Mitteilung von Ivánovics), sondern bei sämtlichen Produkten auch durch ihre chromatographische Untersuchung. Bei der aufsteigenden Chromatographie (Lösungsmittel Phenol–Wasser 7 : 3, Entwicklung mit Ninhydrin) wurden von der Auftragstelle ausgehende, in der Wanderungsrichtung verzogene Streifen gewonnen. Durch weitere fraktionierte Dialyse dieser Produkte dialysierten Fraktionen heraus, deren Chromatogramme bei konstanter Laufzeit (20 Stunden) immer kürzere (von der Auftragstelle ausgehende) Streifen darstellten, bis schliesslich das Chromatogramm des undialysierten Rückstandes aus einem einzigen, auf der Auftragstelle verbliebenen scharf abgegrenzten Fleck bestand.

Die synthetischen γ-Poly-glutaminsäuren binden Wasser und Aschebestandteile sehr hartnäckig, ebenso wie dies beim APP und SPP der Fall ist. Dies hat zwei

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Folgen: erstens lassen sich vollkommen aschefreie Paräparate durch Reinigung mittels einer gewöhnlichen Dialyse kaum gewinnen, und zweitens lässt sich das gebundene Wasser durch Trocknung in der Hochvakuumpistole praktisch genügend schnell nur bei 110–120° entfernen, doch erfolgt bei dieser Temperatur schon eine geringfügige Zersetzung, die auch an der schwachen Verfärbung der schneeweissen Produkte zu erkennen ist. Der Aschegehalt unserer Präparate schwankte zwischen <0,01 und 1,8%. Wegen der grossen Wasserbindungsfähigkeit ist zwar eine strenge Kontrolle der Endprodukte mittels Elementaranalyse nicht möglich, doch liess sich feststellen, dass die bei der Gefriertrocknung anfallenden Produkte nach 24 stündigem Aufbewahren im Vakuumexsiccator über P_2O_5 ziemlich genau 1 Mol. gebundenes Wasser je zwei Glutaminsäurereste enthalten. Tabelle 2 fasst einige Daten der Elementaranalyse zusammen; die Trocknungsart ist in der letzten Spalte verzeichnet.

Es ist hier zu bemerken, dass Waley[14] für seine synthetische γ-Poly-L-glutaminsäure, die ebenfalls durch Gefriertrocknung herausgewonnen wurde, Analysendaten angibt (C 40,9; H 5,9; N 9,55), die für 1 Mol. gebundenes Wasser je ein Glutaminsäurerest (Ber. C 40,8; H 6,2; N 9,5) entsprechen. Eine derartige Zusammensetzung wurde von uns weder beim SPP oder APP, noch bei unseren synthetischen Produkten beobachtet, hingegen wurde dieser Fall bei der synthetischen αγ-Poly-glutaminsäure[10] gefunden. Es ist noch zu bemerken, dass der eine unvollständige Verseifung des Polyesters andeutende geringe Methoxylgehalt einiger Präparate nicht einen unüberwindbaren Fehler der Synthese bedeutet. Wegen den geringen Ansätzen, auf die wir einstweilen angewiesen waren, haben wir—um etwaige Spaltungen der Peptidkette zu vermeiden—die möglichst mildeste Verseifungsart angewandt.

TABELLE 2

Produkt	Herstellungsart S. Tab. 1 No.	C %	H %	N %	CH_3O %	Asche (Sulfat) %	Trocknungsart, über P_2O_5 22 mm
γ-Poly-L-Glu.	2	42,8	5,4				24 Stunden 20°
γ-Poly-L-Glu.	4	44,8	5,7	10,2	0,0	0,0	24 Stunden 20° dann 5 Stunden 110°
γ-Poly-L-Glu.	5	44,2	6,2	10,2	1,5	2,2	24 Stunden 20° dann 1 Stunde 100°
γ-Poly-L-Glu.	6	43,8	6,2		1,0	1,2	8 Stunden 100°
γ-Poly-D-Glu.	7			10,4			24 Stunden 20°
γ-Poly-D-Glu.	8	43,7	6,1	10,3	1,2	0,0	24 Stunden 20°
Subtilis-Polypeptid		43,8	5,5	10,1		0,0	24 Stunden 20°
Ber. $(C_{10}H_{14}O_6N_2 \cdot H_2O)_n$		43,6	5,85	10,2			
Ber. $(C_5H_7O_3N)_n$		46,5	5,5	10,8			

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ANHANG

VERGLEICHENDE SEROLOGISCHE UNTERSUCHUNGEN SYNTHETISCHER POLYGLUTAMINSÄUREN VERSCHIEDENER KONSTITUTION

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Durch wiederholtes intravenöses Impfen von Kaninchen oder Pferden mit durch Hitze getöteten bekapselten Milzbrandbazillen lassen sich Immunsera gewinnen, die mit Lösungen der natürlichen Polyglutaminsäuren bis zu einer Verdünnung von mehreren Millionen eine Präzipitationsreaktion zeigen.[1,2] Unter natürlichen Polyglutaminsäuren ist die aus Milzbrandbacillen (*B. anthracis*) abgetrennte (Anthrax-Polypeptid) und die aus dem Nährboden anderer aëroben, mesophilen Sporenträger (z.B. *B. subtilis*) isolierte Poly-glutaminsäure (Subtilis-Polypeptid) zu verstehen. Beide Polypeptide weisen die Eigenschaft eines Haptens (Halbantigens) auf, d.h. ihre parenterale Verabreichung hat keine Bildung eines Antikörpers zur Folge.[2,3]

Als Ergänzung der Konstitutionsaufklärung des Anthrax-Polypeptids und des Subtilis-Polypeptids, die Bruckner und Mitarbeiter[4] durchgeführt haben, wurden synthetische Poly-glutaminsäuren verschiedener Konstitution auf ihre serologische Aktivität geprüft. Diese Prüfung wurde mit antikapsularen Immunkörper enthaltenden Kaninchen- und Pferdesera durchgeführt; als Vergleichssubstanz diente ein Subtilis-Polypeptid Präparat ursprünglicher Isolierungsart.[5] Die Versuchsergebnisse sind in der Tabelle 1 und 2 angeführt.

Tabelle 1 enthält die Ergebnisse der mit Hilfe der Ringprobe und Agardiffusionsmethode durchgeführten Versuche. Aus diesen Daten ist ersichtlich, dass ein antikapsularen Immunkörper enthaltendes Pferdeserum nur von der γ-Poly-D-glutaminsäure und der *mesoiden* γ-Polyglutaminsäure präzipitiert wurde. Gänzlich inaktiv hingegen, erwiesen sich die Poly-glutaminsäuren anderer Konstitution, darunter auch die γ-Poly-L-glutaminsäure, obzwar diese erste qualitative Testung bei der mässigen Verdünnung von 1 : 1000 durchgeführt wurde. Zu den Daten dieser Tabelle sei noch bemerkt, dass anstatt der durchschnittlichen Molekulargewichte der einzelnen Präparate ihre Aminostickstoffwerte (bestimmt nach van Slyke) verzeichnet wurden.

Die Tabelle 2 berichtet über die quantitative, vergleichende Prüfung der serologischen Aktivität des Subtilis-Polypeptids ursprünglicher Isolierungsart,[5] der γ-Poly-D-glutaminsäure (Tabelle 1, Nr. 1) und der *mesoiden* γ-Polyglutaminsäure (Tabelle 1, Nr. 3). Es ist aus diesen Daten ersichtlich, dass die synthetische γ-Poly-D-glutaminsäure Pferdeimmunsera bei eben so grossen Verdünnungen präzipitiert wie das Subtilis-Polypeptid, gleich sind auch die maximalen Menge des abgeschiedenen Antikörpers. Die *mesoide* γ-Poly-glutaminsäure zeigte gegenüber Pferdeserum eine etwas schwächere Aktivität als die γ-Poly-D-glutaminsäure. Aus dem Kaninchenserum Nr. 46 wurde nur ein Teil seines Antikörpergehaltes durch γ-Poly-D-glutaminsäure präzipitiert. Sonderbarer Weise zeigte das Kaninchenserum-P, dessen mit dem

[1] J. Tomcsik und H. Szongott *Z. ImmunForsch.* **77**, 86 (1933).
[2] J. Tomcsik und G. Ivánovics *Z. ImmunForsch.* **93**, 195 (1938).
[3] G. Ivánovics *Z. ImmunForsch.* **97**, 443 (1939).
[4] V. Bruckner, J. Kovács, J. Wein, M. Kajtár und H. Nagy, s. die vorangehende Mitteilung.
[5] G. Ivánovics und V. Bruckner *Z. ImmunForsch.* **90**, 304 (1937); **91**, 175 (1937).

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TABELLE 1

Konstitution der Poly-glutaminsäure	Art der Synthese (Literaturangabe)	Amino-N %	Serologische Aktivität
(1) γ-Poly-D-Glu.	4 (Methode 2)	1,5	+
(2) γ-Poly-D-Glu.	4 (Methode 4)	0,65	+
(3) *mesoide* γ-Poly-Glu.	4	2,9	+
(4) γ-Poly-L-Glu.	4	0,36	—
(5) α-Poly-L-Glu.	6	0,14	—
(6) α-Poly-D-Glu.	6	0,12	—
(7) αγ-Poly-L-Glu.	7	0,36	—
(8) αγ-Poly-D-Glu.	7	0,43	—

Qualitative Prüfung der serologischen Aktivität von Poly-glutaminsäuren verschiedener Konstitution mit Antianthrax-Pferdeimmunseren. Verdünnung: 10^3.

TABELLE 2

Substanz	Angewandtes Immunserum	Präzipitationstiter (Millionen)	Menge des aus 1 ml Serum präzipitierten Antikörpers (μg)
Subtilis-Polypeptid	Kaninchen-P	0,2	844
	Kaninchen Nr. 46	2,5	1231
	Pferde Nr. 971	2,5	945
	Pferde AS	3,0	1790
γ-Poly-D-Glu.	Kaninchen-P	keine Präz.	
	Kaninchen Nr. 46	2,5	819
	Pferde Nr. 971	2,5	881
	Pferde AS	3,0	1740
mesoide γ-Poly-Glu.	Pferde AS	2,0	1030

Quantitative, vergleichende Prüfung der serologischen Aktivität der γ-Poly-D-glutaminsäure (Tabelle 1, Nr. 1), der *mesoiden* γ-Poly-glutaminsäure (Tabelle 1, Nr. 3) und des Subtilis-Polypeptids (Amino-N 0,20%).

Subtilis-Polypeptid ermittelter Präzipitationstiter übrigens ziemlich niedrig war, mit γ-Poly-D-glutaminsäure überhaupt keine Präzipitationsreaktion. Dass aber der Antikörper dieses vor 15 Jahren hergestellten und seitdem aufbewahrten Immunserums mit γ-Poly-D-glutaminsäure doch spezifisch reagierte konnte, durch ihre positive

[6] V. Bruckner, K. Kovács, J. Kovács und A. Kótai *Experientia* **10**, 166 (1945); *Hung. Acta Chim.* **5**, 267 (1955).

[7] V. Bruckner, M. Szekerke und J. Kovács *Naturwissenschaften* **42**, 179 (1955); **43**, 107 (1956); **44**, 90 (1957); *Z. Physiol. Chem.* **309**, 25 (1957).

Hemmungsreaktion nachgewiesen werden. Bei der Ermittlung dieser Hemmungsreaktion diente als Grundlage die beim optimalen Mengenverhältnis ausgeführte Präzipitationsreaktion des Subtilis-Polypeptids und des Kaninchenserums-P. Diese Reaktion wurde von 150 μg der γ-Poly-D-glutaminsäure gänzlich, von 30 μg teilweise aufgehoben. Vollständigkeitshalber sei hier bemerkt, dass keine der Poly-glutaminsäuren, die in der Tabelle 1 als serologisch inaktiv bezeichnet wurden, die Präzipitationsreaktion des Kaninchenserums-P und des Subtilis-Polypeptids auch in geringstem Mass beeinträchtigte, auch dann nicht, wenn sie in einer Menge von 650 μg augesetzt wurde.

Die oben aufgezählten feineren Unterschiede, die zwischen dem serologischen Verhalten des Subtilis-Polypeptids, der γ-Poly-D-glutaminsäure und der *mesoiden* γ-Poly-glutaminsäure zu beobachten waren, dürften ihren Grund in der Verschiedenheit der durchschnittlichen Molekulargewichte bzw. der Dispersität dieser Polypeptide haben. Diese Unterschiede liessen sich an Hand der Ouchterlony'schen Agar-Diffusionsmethode[8] sehr klar erkennen. Während nämlich im Falle des Subtilis-Polypeptids eine weniger als 1 mm breite, sehr scharf abgegrenzt Präzipitationszone in einem 3 mm Abstand vom Rande der das Immunserum enthaltenden Bohrung entstand, erschien die von der Präzipitations herrührende Trübung z.B. im Falle der synthetischen γ-Poly-D-glutaminsäure in Form eines etwa 3 mm breiten, inhomogenen Streifens, dessen Rand fast ganz bis zum Rand der das Immunserum enthaltenden Bohrung hervorgedrungen war. Aus diesem Unterschied ist darauf zu schliessen, dass das Subtilis-Polypeptid ziemlich homodispers ist, während die synthetische γ-Poly-D-glutaminsäure ein stark polydisperses Gemisch darstellt, dessen überwiegender Anteil aus Komponenten besteht, die ein kleineres Molekulargewicht haben als die überwiegenden Komponenten des Subtilis-Polypeptids. Auf diese Differenz dürfte auch das unterschiedliche Verhalten des Subtilis-Polypeptids und der γ-Poly-D-glutaminsäure gegenüber dem Kaninchenserum-P zurückgeführt werden. Hierzu sei auf die frühere Beobachtung[9,10] hingewiesen, dass Anthrax-Antikörper, abhängig davon, ob sie in Kaninchen oder Pferden entstanden sind, mit ihren homologen Haptenen auf verschiedene Weise reagieren können, und zwar auch dann, wenn ihre Spezifität gleich ist.

Die in Tabelle 2 zusammengefassten Versuchsbefunde sind noch durch die Ergebnisse zu ergänzen, die bei der Untersuchung der durch die serologisch aktiven Polyglutaminsäuren adsorbierten Sera gewonnen wurden. Diesbezügliche Untersuchungen, die mit dem Pferdeserum AS durchgeführt wurden, brachten folgendes Ergebnis. Es ist aus Tabelle 2 ersichtlich, dass die synthetische γ-Poly-D-glutaminsäure aus dem Pferdeserum AS praktisch die gleiche Menge des Antikörpers präzipitiert wie das Subtilis-Polypeptid; (1790 bzw. 1740 μg; die geringe Differenz dürfte dem Versuchsfehler zugeschrieben werden). Aus der Flüssigkeit, die nach dem Abschleudern des Präzipitats gewonnen wurde, konnte weder durch einen Zusatz vom Subtilis-Polyptpeid, noch durch Zusatz von der synthetischen γ-Poly-D-glutaminsäure eine erneute Präzipitation erzeugt werden. Mit der *mesoiden* γ-Poly-glutaminsäure liessen sich zwar nur 1030 μg des Antikörpers abscheiden, doch konnten aus der abgeschleuderten Flüssigkeit durch Zusatz von 25 μg des Subtilis-Polypeptids noch weitere

[8] Ö. Ouchterlony *Acta Path. Microbiol., Scand.* **26,** 507 (1949).
[9] G. Ivánovics *Z. ImmunForsch.* **97,** 443 (1939).
[10] G. Ivánovics *Z. ImmunForsch.* **98,** 420 (1940).

687 μg des Antikörpers ausgefällt werden, so dass die Gesamtmenge 1717 μg betrug. Wurde jedoch mit der mesoiden γ-Poly-glutaminsäure der Antikörper aus dem Pferdeimmunserum nebst Anwendung des optimalen Mengenverhältnisses der beiden Lösungen einmal ausgefällt, so konnte durch Zusatz von *mesoider* γ-Polyglutaminsäure zur abgeschleuderten Flüssigkeit keine weitere Präzipitation erreicht werden.

Zusammenfassend lässt sich nun sagen, dass die serologischen Versuchsbefunde mit den chemischen Untersuchungsergebnissen über die Konstitution des immunspezifischen, polypeptidartigen Haptens der Anthrax-Subtilis Bacillengruppe in vollem Einklang stehen. Überdies weisen diese Versuchsbefunde ein u.E. sehr interessantes Beispiel der Immunspezifität auf. Es ist nämlich aus den Ergebnissen der serologischen Untersuchungen klar ersichtlich, dass die Reaktion des antikapsularen Anthraxantikörpers in bezug auf die Konstitution der Poly-glutaminsäuren strukturspezifisch ist, da von den letzteren nur γ-Poly-glutaminsäuren entsprechender Konfiguration eine serologische Aktivität zeigen, nicht aber α- und αγ-Poly-glutaminsäuren. Weiterhin ist diese Reaktion bis zu einer noch zu ermittelnden Grenze auch stereospezifisch, da von den γ-Poly-glutaminsäuren nur die γ-Poly-D-glutaminsäure und die *mesoide* γ-Poly-glutaminsäure serologisch aktiv sind, während die γ-Poly-L-glutaminsäure keine serologische Aktivität zeigt. Ob die geringere serologische Aktivität der *mesoiden* γ-Poly-glutaminsäure in der Tat auf ihre eigenartige Konstitution, d.h. auf die Anwesenheit von 50% von γ-L-Glutaminsäureresten zurückzuführen ist, muss noch durch weitere Untersuchungen überprüft werden, da die jetzt untersuchte Substanz einen viel grösseren Aminostickstoffgehalt (d.h. vermutlich ein viel geringeres Molekulargewicht) besass, als die γ-Poly-D-glutaminsäure.

METHODISCHES

Das zum Vergleich herangezogene Subtilis-Polypeptid wurde nach dem ursprünglichen Verfahren[3] isoliert.

Die Kaninchen-Immunsera wurden nach dem Verfahren von Tomcsik und Iványovics[2] hergestellt. Eines dieser (Bezeichung: P) war schon im Jahre 1940 hergestellt und seitdem aufbewahrt worden, während das andere (Nr. 46) unmittelbar vor Beginn dieser Untersuchungen hergestellt wurde. Die Pferde-Immunsera wurden vom Institut für Impfstofferzeugung ("Phylaxia", Budapest) im Jahre 1940 hergestellt, und zwar durch Impfung von Pferden mit lebendigen, avirulenten, kapselbildenden Milzbrandbacillen.

Zwecks Ermittlung des Präzipitationstiters wurden aus der Lösung der zu testenden Substanz Verdünnungsreihen nach dem Prinzip der zweifachen Verdünnung bereitet und je 0,2 ml dieser Proben mit je 0,2 ml des 1 : 2 verdünnten Serums versetzt. Inkubation: 48 Stunden bei 4°.

Die serologischen Hemmungsreaktionen wurden der Ermittlung des Präzipitationstiters ähnlich durchgeführt. Proben einer der optimalen Präzipitation entsprechend verdünnten Lösung des Subtilis-Polypeptids wurden zuerst mit verschiedenen Mengen der zu prüfenden Poly-glutaminsäuren, dann mit dem Serum versetzt.

Die quantitativen Präzipitationsproben wurden foglendermassen durchgeführt: in einem abgekühlten Zentrifugenrohr wurden 1 ml Serum und 25 μg der zu prüfenden Substanz in 1 ml Lösung gemischt das Gemisch 48 Stunden im Eisschrank aufbewahrt, dann das Präzipitat abgeschleudert und danach durch Aufschlämmen und wiederholtes Abschleudern zweimal mit je 5 ml eiskaltem Salzwasser gewaschen. Der so

gewonnene Niederschlag wurde nach der Methode von Cleghorn und Jendrassik[11] aufgeschlossen und sein Stickstoffgehalt mit Nessler's Reagens durch drei Parallelbestimmungen ermittelt. Als Menge des präzipitierten Antikörpers wurde das Produkt Stickstoff μg 6,25 bezeichnet.

Die Diffusion der Polypeptide wurde nach der Methode von Ouchterlony[8] in einem aus 1% Agar enthaltendem, abgepuffertem Salzwasser bereiteten Agargel untersucht. Die Ränder der das Serum bzw. die Lösung der zu testenden Substanz enthaltenden zwei Bohrungen hatten einen Abstand von 9 mm.

[11] R. A. Cleghorn und J. Jendrassik *Biochem. Z.* **274**, 189 (1934).

Tetrahedron, 1958, Vol. 2, pp. 241–245. Pergamon Press Ltd., London

STUDIES IN HALOCHALCONES AND RELATED COMPOUNDS: SYNTHESIS OF 3′:5′–DICHLORO–2′–HYDROXYCHALCONES AND THEIR DERIVATIVES

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Abstract—The condensation of 3:5-dichloro-2-hydroxy acetophenone with various aldehydes afforded chalcones, which were converted into the corresponding 6:8-dichloroflavanones by the action of dilute ethanolic hydrochloric acid. The oxidation of chalcones by means of selenium dioxide and by alkaline hydrogen peroxide gave 6:8-dichloro-flavones and -flavonols respectively. Incidentally, some chalcones from 3:5-dichloro-2-methoxyacetophenone were also prepared.

ALTHOUGH a considerable amount of work has appeared describing the synthesis of the chalcones and related compounds containing the hydroxy and alkoxy groups in different positions, those containing other substituents have been comparatively less synthesised. Some chalcones and flavonoid compounds containing alkyl,[1] amino- and acetamino-,[2] carboxyl-,[3] nitro-[4] and mono-halo-[5] groups have been described in the literature. Chalcones containing two halo-groups in the ketonic part of the molecule seem to have been hardly studied. That such compounds may possess bacteriostatic activity adds to the interest of this work. As a part of the comprehensive study of the dihalochalcones and the related heterocyclic compounds, the synthesis of 3′:5′-dichloro-2′-hydroxychalcones and the corresponding 6:8-dichloroflavonoid derivatives have been described in this communication.

3:5-dichloro-2-hydroxyacetophenone was condensed smoothly with benzaldehyde in presence of 40% alcoholic alkali. The product obtained was identified as 3′:5′-dichloro-2′-hydroxy chalcone (I) as (a) it gave a characteristic deep-red colour with concentrated sulphuric acid and red-brown colour with alcoholic ferric chloride, (b) it dissolved in sodium hydroxide with yellow coloration and (c) it gave acetyl and benzoyl derivatives confirming the presence of the free hydroxy group.

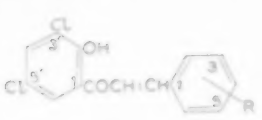
This chalcone was cyclised to the 6:8-dichloroflavanone (II) by means of dilute ethanolic hydrochloric acid.[6] Further, it was oxidised directly by means of selenium

[1] S. D. Limaye *et al.* *Rasayanam* **2**, 53–96 (1955); *Chem. Abstr.* **50**, 11331 (1956).
[2] F. Kunckell *et al.* *Ber. Dtsch. Chem. Ges.* **37**, 2826 (1904); *Ber. Dtsch. Chem. Ges.* **46**, 2678 (1913); M. Scholtz and L. Huber *Ber. Dtsch. Chem. Ges.* **37**, 390 (1904); D. H. Marrian, P. B. Russell and A. R. Todd *J. Chem. Soc.* 1419 (1947); A. A. Raval and N. M. Shah *J. Org. Chem.* **21**, 1408 (1956).
[3] T. Nagano and K. Matsumura *J. Amer. Chem. Soc.* **75**, 6237 (1953); D. N. Shah, S. K. Parikh and N. M. Shah *J. Amer. Chem. Soc.* **77**, 2223 (1955); G. N. Vyas and N. M. Shah *J. Indian Chem. Soc.* **28**, 43 (1951).
[4] C. Engler and K. Dorant *Ber. Dtsch. Chem. Ges.* **28**, 2497 (1895); H. Rupe and D. Wasserzug *Ber. Dtsch. Chem. Ges.* **34**, 3527 (1901); I. Tanasecu and A. Baciu *Chem. Abstr.* **32**, 1674 (1938); H. S. Mehra and K. B. Mathur *J. Indian Chem. Soc.* **33**, 618 (1956).
[5] W. Feuerstein and St. V. Kostanecki *Ber. Dtsch. Chem. Ges.* **31**, 717 (1898); E. Schrautstatter and S. Deutsch *Chem. Ber.* **81**, 489 (1948); F. C. Chen and C. H. Yang *Chem. Abstr.* **49**, 2432 (1955).
[6] St. V. Kostanecki and W. Szabranski *Ber. Dtsch. Chem. Ges.* **37**, 2634 (1904); T. A. Geissman and R. O. Clinton *J. Amer. Chem. Soc.* **68**, 697 (1946).

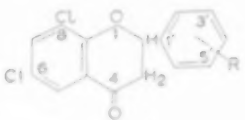
dioxide[7] in *iso*amyl alcohol to 6:8-dichloroflavone (III, R = H) and by cold alkaline hydrogen peroxide[8] to 6:8-dichloroflavonol (IV, R = —OH).

Also 3:5-dichloro-2-methoxy acetophenone (m.p. 42°) has been condensed with 2-methoxy-, 4-methoxy- and 3:4-dimethoxy- benzaldehydes by keeping the reaction mixture for 90–100 hr, and the chalcones isolated were found to be identical with the methoxy derivatives listed in Table 1 (nos. 7, 13, 24 *or* 10, 17 and 27 respectively).

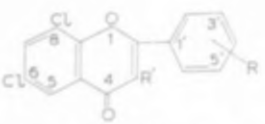
Other chalcones containing substituents in the styryl components and their flavonoid derivatives were prepared similarly. Thus, the chloro-groups in 3- and 5-positions of 2-hydroxyacetophenone nucleus do not hinder the formation of chalcones, which could also be smoothly converted into the 6:8-dichloroflavonoid compounds. This is in conformation with the other substituted chalcones studied.



(I)



(II)



(III R' = H and OH)

EXPERIMENTAL

All melting points are uncorrected.

3:5-*Dichloro-2-hydroxyacetophenone* (m.p. 97°) was prepared by the Fries isomerisation of 2:4-dichloro phenyl acetate (1 mole) by means of anhydrous aluminium chloride (3·3 moles) at 150° for 2 hr (Yield: 55 per cent). Found: Cl, 34·21. Calc. for $C_8H_6O_2Cl_2$: Cl, 34·63.

General procedures

Chalcone (I) Caustic potash (30 ml 40 per cent) was added to a homogeneous solution of 3:5-dichloro-2-hydroxyacetophenone (2 g, 1 mole) and the aldehyde (1 mole) in ethyl alcohol (25–30 ml) with continuous shaking. The coloured reaction mixture was kept overnight at room temperature (25–30°) after heating for 5–10 min on a water-bath, when the reddish colour of the reaction mixture deepened considerably. On dilution with ice-cold water and acidifying with hydrochloric acid (1 : 1), the solid separated. It was collected, washed with dilute sodium bicarbonate solution and crystallised. In case of the chalcones, serial no. 4, 11, 21 and 24 the reaction mixture was left at room temperature for 100 hr. All chalcones gave a characteristic deep red colour with concentrated sulphuric acid.

The *benzoyl* derivative or the *acetyl* derivative was prepared by heating a mixture of the chalcone, benzoyl chloride *or* acetic anhydride and few drops of pyridine. The reaction mixture after dilution with acidulated water gave a solid which was crystallised.

[7] K. Venkataraman *et al.* *J. Chem. Soc.* 866 (1935); 569 (1936); D. Chakravarti and J. Dutta *J. Indian Chem. Soc.* **16**, 639 (1939).
[8] J. Algar and J. Flynn *Proc. R. Irish Acad.* B **42**, 1 (1934); *Chem. Abstr.* **29**, 1616 (1935).

The *methoxy* derivative was prepared by refluxing at 70° a mixture of the chalcone, dimethyl sulphate, potassium carbonate (fused) and acetone (solvent) for 4–6 hr. The solid was crystallised after dilution and finally washing with acidulated water.

Flavanone (II) A hot solution of 3′:5′-dichloro-2′-hydroxy-chalcone (0·5 g) in ethanol (50 ml) was treated with hydrochloric acid (15 ml, 10 per cent) till a distinct turbidity appeared. Enough ethanol (10–15 ml) was then added to get a clear solution, which was refluxed on a water-bath for 45–50 hr. On removal of ethanol, the remaining liquid gave a solid, which crystallised from ethanol. Yield: 0·2–0·3 g. It gave a reddish colour with concentrated sulphuric acid.

TABLE I. 3′-5′-DICHLORO-2′-HYDROXY CHALCONES (I)

Serial no.	Substituent	Colour and shape of crystals	Melting point (°C)	Formula	% chlorine	
					Calc.	Found
1.	Nil	Orange needles	143	$C_{15}H_{10}O_2Cl_2$	24·23	24·13
2.	Benzoyl of (1)	White plates	101	$C_{22}H_{14}O_3Cl_2$	17·88	17·70
3.	Acetyl of (1)	Yellow needles	67	$C_{17}H_{12}O_3Cl_2$	20·98	21·19
4.	2-Hydroxy	Yellowish-green shining needles (*a*)	195	$C_{15}H_{10}O_3Cl_2$	22·98	22·72
5.	Dibenzoyl of (4)	White granules (*a*)	150	$C_{29}H_{18}O_5Cl_2$	13·74	14·06
6.	Diacetyl of (4)	Yellowish prisms (*a*)	105	$C_{19}H_{14}O_5Cl_2$	18·07	17·98
7.	Dimethoxy of (4)	Discoloured granules	215	$C_{17}H_{14}O_5Cl_2$	20·11	20·31
8.	2-Methoxy	Yellow granules	143	$C_{16}H_{12}O_3Cl_2$	21·99	22·10
9.	Benzoyl of (8)	Yellow needles	81	$C_{23}H_{16}O_4Cl_2$	16·63	16·48
10.	Methoxy of (8)	Discoloured granules	215	identical	with	(7)
11.	4-Hydroxy	Shining yellow plates (*a*)	160	$C_{15}H_{10}O_3Cl_2$	22·98	22·73
12.	Dibenzoyl of (11)	White needles (*a*)	107	$C_{29}H_{18}O_5Cl_2$	13·74	13·87
13.	Dimethoxy of (11)	Golden-yellow fine needles	120	$C_{17}H_{14}O_5Cl_2$	20·11	20·00
14.	4-Methoxy	Orange needles (*a*)	165	$C_{16}H_{12}O_3Cl_2$	21·99	21·87
15.	Benzoyl of (14)	Pale-yellow granules (*a*)	105	$C_{23}H_{16}O_4Cl_2$	16·63	16·44
16.	Acetyl of (14)	Shining yellow granules	101	$C_{18}H_{14}O_4Cl_2$	19·45	19·35
17.	Methoxy of (14)	Golden-yellow small needles	120	identical	with	(13)
18.	3:4-methylenedioxy	Yellow granules (*a*)	195	$C_{16}H_{10}O_4Cl_2$	21·07	20·9
19.	Benzoyl of (18)	Shining yellow needles (*a*)	201	$C_{23}H_{14}O_5Cl_2$	15·89	16·10
20.	Acetyl of (18)	Yellow needles (*a*)	114	$C_{18}H_{12}O_5Cl_2$	18·74	18·50
21.	3-Methoxy-4-hydroxy	Deep-orange needles	195	$C_{16}H_{12}O_4Cl_2$	20·94	21·42
22.	Dibenzoyl of (21)	Yellowish-white needles	95	$C_{30}H_{20}O_6Cl_2$	12·98	12·83
23.	Diacetyl of (21)	Colourless granules (*c*)	120	$C_{20}H_{16}O_6Cl_2$	16·79	16·66
24.	Trimethoxy of (21)	Yellowish-white rectangular plates (*c*)	100	$C_{18}H_{16}O_4Cl_2$	19·35	19·11
25.	3:4-Dimethoxy	Orange needles (AcOEt)	144	$C_{17}H_{14}O_4Cl_2$	20·11	19·98
26.	Acetyl of (25)	Yellow needles	110	$C_{19}H_{16}O_5Cl_2$	17·98	17·73
27.	Methoxy of (25)	Yellowish-white rectangular plates (*c*)	100	identical	with	(24)
28.	2-Chlore	Yellow granules	137	$C_{15}H_9O_2Cl_3$	32·57	32·10
29.	Acetyl of (28)	Yellow needles (acetone)	112	$C_{17}H_{11}O_3Cl_3$	28·86	28·41
30.	Benzoyl of (28)	Yellow shining plates	115	$C_{22}H_{13}O_3Cl_3$	24·71	24·23

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Flavone (III, R = H) Selenium dioxide (0·4 g) was added to 3′:5′-dichloro-2′-hydroxychalcone (0·5 g) dissolved in dry *iso*amyl alcohol (20–25 ml) and the mixture was refluxed at 150–160° for about 15 hr ($CaCl_2$ guard tube). The precipitated selenium was, then filtered and the filtrate was subjected to steam distillation to remove *iso*amyl alcohol. The brownish solid obtained on cooling the residual liquid in the flask, was crystallised as yellowish crystals. Yield: 0·2–0·3 g.

Flavonol (III, *R = OH*). To a solution of the chalcone (0·4 g) in ethanol (25 ml), sodium hydroxide solution (25 ml, 5 per cent) was added. The red solution was treated with hydrogen peroxide (5–7 ml, 18 per cent) after thoroughly cooling in the ice-bath and left for 3–4 hr. A solid began to separate and the colour of the solution slowly changed to yellow. The reaction mixture was then left overnight at room temperature (25–30°). On dilution with ice-cold water and acidification by dilute hydrochloric acid, a yellow solid separated which was crystallised from ethanol. Yield: 0·2–0·3 g. Flavonol was soluble in dilute sodium hydroxide giving a pale yellow solution.

Table 2. 6:8-Dichloro-flavanones (II)

Serial no.	Substituent	Colour and shape of crystals	Melting point (°C)	Formula	% chlorine	
					Calc.	Found
31.	Nil	Yellowish-white plates	115	$C_{15}H_{10}O_2Cl_2$	24·23	23·93
32.	2′-Hydroxy	Shining plates	90	$C_{15}H_{10}O_3Cl_2$	22·98	22·79
33.	2′-Methoxy	Yellow shining plates	105	$C_{16}H_{12}O_2Cl_2$	21·99	21·87
34.	4′-Hydroxy	Yellowish prismatic needles	95	$C_{15}H_{10}O_3Cl_2$	22·98	22·51
35.	4′-Methoxy	Brownish plates	118	$C_{16}H_{12}O_2Cl_2$	21·99	21·89
36.	3′:4′-methylenedioxy	Discoloured granules	255	$C_{16}H_{10}O_4Cl_2$	21·07	20·93
37.	3′-Methoxy-4′-hydroxy	Faint-yellow granules	165	$C_{16}H_{12}O_4Cl_2$	20·94	20·67
38.	3′:4′-dimethoxy	Yellowish fine needles	75	$C_{17}H_{14}O_4Cl_2$	20·11	19·67
39.	2′-Chloro	Yellowish fine needles	135	$C_{15}H_8O_2Cl_3$	32·52	32·02

Table 3. 6:8-Dichloro-flavones (III, R = H)

Serial no.	Substituent	Colour and shape of crystals	Melting point (°C)	Formula	% chlorine	
					Calc.	Found
40.	Nil	White needles	154	$C_{15}H_8O_2Cl_2$	24·40	24·05
41.	2′-Hydroxy	Discoloured granules	240	$C_{15}H_8O_3Cl_2$	23·13	22·91
42.	2′-Methoxy	Yellowish-white needles	160	$C_{16}H_{10}O_3Cl_2$	22·12	21·92
44.	4′-Hydroxy	Pale-yellow granules (*b*)	200	$C_{15}H_8O_3Cl_2$	23·13	22·96
44.	4′-Methoxy	Yellow short needles	187	$C_{16}H_{10}O_3Cl_2$	22·12	21·92
45.	3′:4′-methylenedioxy	Yellow needles	230	$C_{16}H_8O_4Cl_2$	21·19	21·09
46.	3′-methoxy-4′-hydroxy	Yellowish-white granules	147	$C_{16}H_{10}O_4Cl_2$	21·07	20·98
47.	3′:4′-Dimethoxy	Yellowish-white needles	225	$C_{17}H_{12}O_4Cl_2$	20·23	20·01
48.	2′-Chloro	White granules	190	$C_{15}H_7O_2Cl_3$	32·71	32·5

The *acetyl* derivative of flavonol was prepared by acetic anhydride–pyridine method, and was crystallised from ethanol. It is insoluble in sodium hydroxide.

All the compounds are tabulated in Tables 1–4. The solvent for crystallisation, unless otherwise mentioned, was ethanol (95 per cent) in each case. Where another solvent has been used, it is indicated in tables by letters in parenthesis along with the colour and shape of crystals (*a*, acetic acid, *b*, benzene and *c*, petrol ether b.p. 60–80°).

TABLE 4. 6:8-DICHLORO-FLAVONOLS (III, R = OH)

Serial no.	Substituent	Colour and shape of crystals	Melting point (°C)	Formula	% chlorine	
					Calc.	Found
49.	Nil	White shining plates	187	$C_{15}H_8O_3Cl_2$	23·13	22·95
50.	Acetyl of (49)	Yellowish needles	157	$C_{17}H_{10}O_4Cl_2$	20·3	20·18
51.	2′-Hydroxy	White needles	222	$C_{15}H_8O_4Cl_2$	21·99	21·90
52.	Acetyl of (51)	White granules	120	$C_{19}H_{12}O_6Cl_2$	17·45	17·25
53.	2′-Methoxy	Whitish-yellow needles	228	$C_{16}H_{10}O_4Cl_2$	21·07	20·97
54.	Acetyl of (53)	Yellow prismatic needles	161	$C_{18}H_{12}O_5Cl_2$	18·74	18·64
55.	4′-Hydroxy	White granules	220	$C_{15}H_8O_4Cl_2$	21·99	21·25
56.	Acetyl of (55)	White granules	145	$C_{19}H_{12}O_6Cl_2$	17·45	17·21
57.	4′-Methoxy	Orange needles	222	$C_{16}H_{10}O_4Cl_2$	21·07	20·91
58.	Acetyl of (57)	Fine yellow needles	176	$C_{18}H_{12}O_5Cl_2$	18·74	18·53
59.	3′:4′-methylene dioxy	Yellow granules	280	$C_{16}H_8O_5Cl_2$	20·33	20·00
60.	Acetyl of (59)	Yellowish needles	230	$C_{18}H_{10}O_6Cl_2$	18·07	18·09
61.	3′-Methoxy-4′-hydroxy	Yellowish-white granules	215	$C_{16}H_{10}O_5Cl_2$	20·11	19·97
62.	Acetyl of (61)	Yellowish-fine needles	136	$C_{20}H_{14}O_7Cl_2$	16·25	16·22
63.	3′:4′-dimethoxy	Yellow granules	215	$C_{17}H_{12}O_5Cl_2$	19·35	19·21
64.	Acetyl of (63)	Yellow needles	195	$C_{19}H_{14}O_6Cl_2$	17·36	17·23
65.	2′-Chloro	Clusters of white needles	194	$C_{15}H_7O_3Cl_3$	31·18	30·93
66.	Acetyl of (65)	Yellowish-white granules	182	$C_{17}H_9O_4Cl_3$	27·76	27·33

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TRITERPENOIDS—LIV

THE CONSTITUTION OF ALNUSENONE

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Abstract—The constitution and stereochemistry of alnusenone have been established and a partial synthesis of alnusenone (II) from friedelin is described. Taraxerone (I) and alnusenone (II) probably represent stabilised intermediates in the biogenesis of friedelin (XV) from squalene.

The unsaturated pentacyclic ketone alnusenone accompanies the isomeric taraxerone in the unsaponifiable matter from alder bark.[1,2,3] The carbonyl group in alnusenone is not hindered since the ketone forms an oxime[3] and on reduction with either lithium aluminium hydride[1,3] or sodium and alcohol[3] it gives a secondary alcohol, alnusenol, which readily forms esters and which is reconverted into alnusenone on oxidation.[3] We consider that the hydroxyl group in alnusenol is equatorial because the alcohol is recovered in high yield after prolonged treatment with sodium amyloxide in air at 170°.

The ethylenic bond in alnusenone is not conjugated with the carbonyl group since alnusenone does not show the characteristic ultra-violet and infra-red absorption spectra of an $\alpha\beta$-unsaturated ketone[3,4] and it is unhindered because alnusenyl acetate is easily reduced to the saturated alnusanyl acetate;[3] alnusenyl acetate readily gives an epoxide on oxidation with monoperphthalic acid. An indication that the ethylenic bond in alnusenone is trisubstituted was afforded by the intensity of short wavelength ultra-violet absorption of alnusenyl acetate[3] and by the infra-red absorption spectrum of the acetate (in carbon disulphide) which includes a band at 788 cm^{-1}. The trisubstituted nature of the double bond in alnusenyl acetate is supported by the following observations. Oxidation of the acetate with osmic acid followed by acetylation gives a saturated triol diacetate which is stable to chromic-acetic acid mixture at room temperature.

As stated above, alnusenone occurs in alder bark associated with the isomeric taraxerone (I) and mixtures of the two ketones are difficult to seperate. These facts led us to make two assumptions which guided further experiment and, in the event, transpired to be justified. First, we assumed a biogenetic relationship between alnusenone and taraxerone and secondly, we assumed that the carbonyl group in alnusenone is at position 3 in an oleanane or modified oleanane carbocyclic structure. The validity of the first assumption was established by the discovery that the hydrocarbon alnusene,[3,4] obtained from alnusenone by the Wolff–Kishner method, is isomerised by mineral acid to a crystal mixture of olean-13(18)-ene (VI) and 18α-olean-12-ene (VII) identical with the hydrocarbon mixture obtained by similar treatment of olean-12-ene (β-amyrene), olean-13(18)-ene, olean-18-ene (germanicene) and friedelene.[5]

[1] S. Chapon and S. David *Bull. Soc. Chim. Fr.* 333 (1953).
[2] S. Chapon and S. David *C.R. Acad. Sci., Paris* **238**, 1600 (1954).
[3] J. M. Beaton, F. S. Spring and R. Stevenson *J. Chem. Soc.* 2616 (1955).
[4] S. Chapon *Bull. Soc. Chim. Fr.* 1076, 1630 (1955).
[5] G. Brownlie, M. B. E. Fayez, F. S. Spring, R. Stevenson and W. S. Strachan *J. Chem. Soc.* 1377 (1956).

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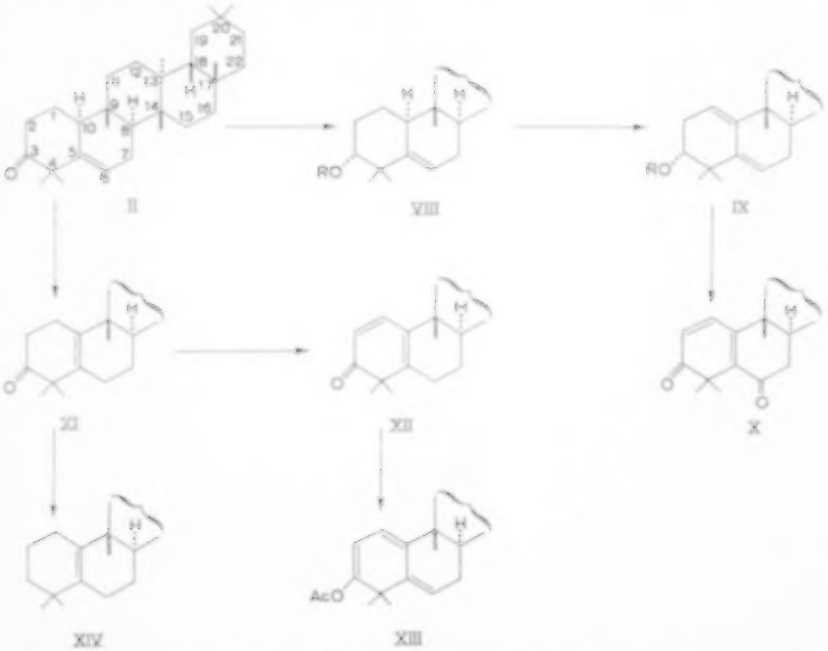
Further information concerning the immediate environment of the trisubstituted double bond in alnusenone was obtained from a consideration of the behaviour of alnusenyl acetate with selenium dioxide. The product of this reaction is an alnusadienyl acetate, the ultra-violet absorption spectrum of which shows it to contain a hetero-annular diene system.[4] Partial catalytic reduction of alnusadienyl acetate gives alnusenyl acetate and complete reduction gives alnusanyl acetate, so establishing that the formation of alnusadienyl acetate from alnusenyl acetate does not involve a molecular rearrangement.

At an early stage of this study a difference was noted between the intensity of the short wavelength ultra-violet absorption of alnusenyl acetate which, as stated earlier, is typical of a trisubstituted double bond and that of alnusenone. In the spectrum of alnusenyl acetate there is a rapid fall in intensity between 2100 and 2300 Å whereas there is a much less marked intensity decrease for alnusenone. This we attribute to a close proximity of the carbonyl group and double bond in alnusenone.

	ε at					
	2050	2100	2150	2200	2300	2400 Å
Alnusenone	3500	2600	1700	1200	400	0
Alnusenyl acetate	3300	2300	950	0	0	0

Assuming that the carbonyl oxygen in alnusenone is attached to C_3 the considerations discussed above lead to the view that the ketone is either (II) or (III). Of these the latter is excluded and the former is supported by the following facts. Alnusenone is not isomerised to an α/β-unsaturated ketone by either alkali or mineral acid. Treatment of alnusenone with *iso*propenyl acetate gives an enol acetate which does not contain a conjugated diene system since it does not show high intensity absorption in the ultra-violet region above 2200 Å; alkaline hydrolysis of the enol acetate regenerates alnusenone. Moreover pyrolysis of alnusenyl benzoate gives a hydrocarbon which is not a conjugated diene since it does not show high intensity absorption above 2200 Å. Alnusenone is therefore formulated as (II) (alnus-5-en-3-one) and the enol acetate as (IV). The hydrocarbon obtained by Wolff–Kishner reduction of alnusenone is alnus-5-ene (V) and the mineral acid isomerisation of this hydrocarbon is represented as a "back-bone" rearrangement induced by protonation of the 5:6-double bond followed by migration of the axial groups or atoms attached to C_{10}, C_9, C_8, C_{14}, and C_{13} to C_5, C_{10}, C_9, C_8, and C_{14} respectively and elimination of a proton from C_{12} and/or C_{18} to give olean-12-ene and/or olean-13(18)-ene. Either of these hydrocarbons is known[5] to give an equilibrium mixture of olean-13(18)-ene (VI) and 18α-olean-12-ene (VII) when treated with mineral acid. Since the hydroxyl group in alnusenol is equatorial we represent this alcohol as alnus-5-en-3α-ol (VIII) and alnusadienyl acetate as alnusa-1(10):5-dien-3α-yl acetate (IX; R = Ac).



Evidence supporting the view that alnusenone is (II) was obtained as follows. Hydrolysis of alnusa-1(10):5-dien-3α-yl acetate using lithium aluminium hydride gives alnusa-1(10):5-dien-3α-ol (IX; R = H) which, like the parent acetate, exhibits the ultra-violet absorption spectrum of a conjugated heteroannular diene with a principal maximum at 2390 Å (ε = 17,000) and subsidiary maxima at 2320 and 2480 Å.

In an attempt to prepare the ketone corresponding to the 1(10):5-dienol, which, it was anticipated, should readily isomerise to a fully conjugated dienone, the dienol was oxidised with chromic acid-pyridine complex at room temperature. The product of the reaction, however, is a yellow-coloured compound, $C_{30}H_{44}O_2$, the ultra-violet absorption spectrum of which shows maxima at 2180 ($\varepsilon = 11{,}000$) and 3190 Å ($\varepsilon = 8300$) and we represent this compound as alnusa-1:5(10)-diene-3:6-dione (X). The dienyl acetate (IX; R = Ac) is not oxidised by chromic acid-pyridine complex at room temperature.

We now turn to a consideration of the behaviour of alnusenone with mineral acid. Chapon[1] converted alnusenone into an isomeric "ketone-II" by relatively mild treatment with sulphuric–acetic acid mixture. Wolff–Kishner reduction of "ketone-II" gave the "hydrocarbon-II" and reduction of "ketone-II" with lithium aluminium hydride gave "alcohol-II" which was characterised by the formation of its acetate. We have obtained "ketone-II" by treatment of alnusenone with hydrochloric–acetic acid mixture, and from this ketone the related "alcohol-II" and its acetate were prepared. The constants of the last two compounds differ appreciably from those previously reported.[4] The infra-red absorption spectrum of the "acetate-II" confirms the view[4] that its double bond is fully substituted. The double bond in "ketone-II" is still in the near neighbourhood of the carbonyl group since successive treatment of "ketone-II" with bromine and potassium acetate yields a compound, $C_{30}H_{46}O$, the absorption spectrum of which shows a maximum at 3220 Å indicating the presence of a fully conjugated dienone chromophore. The infra-red absorption spectrum (in Nujol) of the dienone $C_{30}H_{46}O$, includes a strong carbonyl band at 1670 cm^{-1}. Accordingly we represent "ketone-II" as alnus-5(10)-en-3-one (XI), and the conjugated dienone as alnusa-1:5 (10)-dien-3-one (XII). Treatment of alnusa-1:5(10)-dien-3-one with *iso*propenyl acetate gives an enol acetate (XIII) the ultra-violet absorption spectrum of which includes a band at 3160 Å ($\varepsilon = 9100$). "Hydrocarbon-II" obtained by Wolff–Kishner reduction of alnus-5(10)-en-3-one is alnus-5(10)-ene (XIV) and like alnus-5-ene (V) it is smoothly isomerised to a mixture of olean-13(18)-ene (VI) and 18α-olean-12-ene (VII) when treated with hydrochloric-acetic acid.

Treatment of alnus-5(10)-en-3-one (XI) with mineral acid, using conditions which convert alnus-5(10)-ene into the mixture of olean-13(18)-ene and 18α-olean-12-ene, gives a complex mixture which does not contain any appreciable quantity of olean-13 (18)-en-3-one. We attribute the difference in behaviour towards mineral acid between alnusene and alnusenone to the proximity of the ethylenic bond and the carbonyl group in the latter.

Chapon and David[2] have reported that treatment of the new pentacyclic ketone from alder bark with osmic acid in chloroform gives taraxerone in a yield which, although variable, is never less than 28 per cent. The French authors were aware that the former ketone is very difficult to separate from taraxerone and were at pains to ensure that the specimen employed for this reaction was homogeneous. They also report that a similar isomerisation was observed by treatment of alnusenyl acetate with osmic acid, presumably giving taraxeryl acetate. We have not been able to repeat these isomerisations and, as stated earlier, we find that treatment of alnusenyl acetate with osmic acid followed by acetylation gave a saturated triol diacetate together with unchanged alnusenyl acetate. If the view, which is discussed later, that the C_{10}-hydrogen atom in alnusenone is α-orientated is correct it follows that the equatorial

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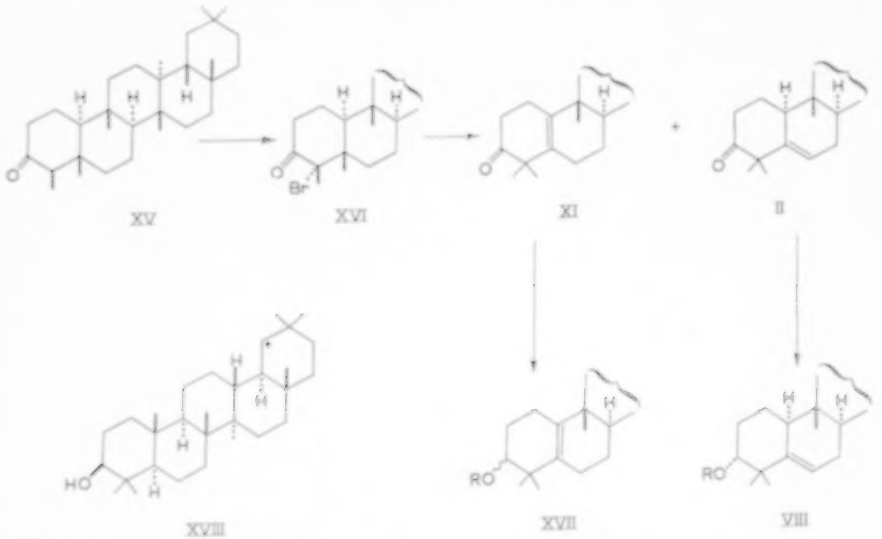
hydroxyl group in alnusenol is also α-orientated in which case the mechanism whereby alnusenyl acetate is converted into taraxeryl acetate, a 3β-acetate, is obscure.*



The derivation of the structure (II) for alnusenone connotes a close relationship between this compound and friedelin (XV), the saturated pentacyclic ketone isolated from cork.[6,7] In a preliminary communication Corey and Ursprung[7] described the formation of 4-bromofriedelin (XVI) by the action of bromine on friedelin enol benzoate and they showed that the bromine atom in 4-bromofriedelin is axial. The position of the bromine atom in 4-bromofriedelin was deduced from its reaction with silver acetate which gives an unsaturated ketone, m.p. 247–248°, $[\alpha]_D$ — 48·6° which "is not isomerised to a conjugated structure" and which was formulated as (II), i.e. the structure now proposed for alnusenone. We have again prepared the unsaturated ketone from 4-bromofriedelin but we find, however, that this reaction product is a mixture since, on reduction with lithium aluminium hydride followed by acetylation, it gives a mixture of alnusenyl acetate (VIII, R = Ac) and alnus-5(10)-enyl acetate (XVII, R = Ac) which is readily separated into its components by crystallisation. Furthermore, crystallisation of a mixture of two parts of alnus-5(10)-en-3-one (m.p. 250–252°, $[\alpha]_D$ — 90°) (XI) and one part of alnusenone (m.p. 245–246°, $[\alpha]_D$ + 31°) (II) gave a ketone mixture, m.p. 247–249°, $[\alpha]_D$ — 51° which is identical with the product (m.p. 247–249°, $[\alpha]_D$ — 52°) obtained from 4-bromofriedelin. The conversion of 4-bromofriedelin into alnusenyl acetate constitutes a partial synthesis of alnusenone from friedelin since alnusenyl acetate is readily converted into alnusenone by hydrolysis and oxidation.[3] The conversion of 4-bromofriedelin into alnusenone shows that friedelin and alnusenone have the same configuration at C_{10}. Furthermore, the formation of alnus-5(10)-en-3-one (XI) from 4-bromofriedelin by an ionic reaction

* Since the completion of our experiments Dr. David has kindly informed us that, starting from a pure sample of alnusenone, he has not been able to repeat the conversion into taraxerone. It would appear that the ketone used by Chapon and David,[2] and named "glutinone" by them, was not homogeneous.

[6] G. Brownlie, F. S. Spring, R. Stevenson and W. S. Strachan *J. Chem. Soc.* 2419 (1956).

[7] E. J. Corey and J. J. Ursprung *J. Amer. Chem. Soc.* **77**, 3667, 3668 (1955); **78**, 5041 (1956).

is strong support for the view that the 5-methyl group and the 10-hydrogen atom in friedelin are axially bonded.

The identification of alnusenone supports currently accepted views[8] on the biogenesis of the pentacyclic triterpenoids from a squalenoid precursor via a common ion (XVIII) or its equivalent. The degeneration of this ion may give rise to germanicol, olean-13(18)-enol, β-amyrin, taraxerol (taraxerone), *epi*alnusenol (whence alnusenone) and friedelin and, accordingly, alnusenone is represented as a stabilised intermediate in the biogenesis of friedelin.

EXPERIMENTAL*

Treatment of alnusenyl acetate with sodium amyloxide. Sodium (1·5 g) was added to a solution of alnusenyl acetate (500 mg) in amyl alcohol (60 cm³) and the mixture refluxed for 17 hr. The product, isolated in the usual way, was heated with acetic anhydride and pyridine at 100° for 30 min. Crystallisation from chloroform–methanol gave alnusenyl acetate as needles (420 mg), m.p. and mixed m.p. 233–235°, $[\alpha]_D + 45°$.

Treatment of alnusenyl acetate with monoperphthalic acid. A solution of alnusenyl acetate (250 mg) in chloroform (25 cm³) at 0° was treated with a solution of monoperphthalic acid (1·2 mole) in ether and the mixture kept at 0° for 18 hr. The product, obtained in the usual way, crystallised from chloroform–methanol to give 5ξ : 6ξ-*epoxyalnusan*-3α-*yl acetate* (190 mg) as needles m.p. 225–227°, $[\alpha]_D \pm 0°$, +1·8° (Found: C, 79·4; H, 10·95; $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8 per cent). It does not give a colour with tetranitromethane in chloroform and it does not show selective absorption between 2000 and 3000 Å.

The epoxide was unchanged (m.p. and mixed m.p. 224–227°, $[\alpha]_D + 2°$) after refluxing for 2 hr with excess lithium aluminium hydride in ether, followed by acetylation of the product, and it was also recovered unchanged (m.p. and mixed m.p. 224–227°, $[\alpha]_D$ 0°), after shaking its acetic acid solution with platinum and hydrogen for 5 hr.

Treatment of alnusenyl acetate with osmium tetroxide. Osmium tetroxide (350 mg) in ether (5 cm³) was added to a solution of alnusenyl acetate (507 mg) in pyridine (50 cm³) and the mixture kept in the dark for 21 days at room temperature. After dilution with ether, the mixture was refluxed for 1 hr with lithium aluminium hydride (750 mg). The product was isolated in the usual manner and treated with acetic anhydride and pyridine for 18 hr at room temperature. A solution of the dry acetylated product in light petroleum–benzene (9 : 1; 70 cm³) was chromatographed on alumina (15 g). Light petroleum–benzene (9 : 1; 300 cm³) eluted fractions which crystallised from chloroform–methanol to give alnusenyl acetate (85 mg) as needles, m.p. and mixed m.p. 232–235°, $[\alpha]_D + 43°$. Light petroleum–benzene (1 : 1; 400 cm³) and benzene (400 cm³) eluted fractions which crystallised from chloroform–methanol to give 3α : 6ξ-*diacetoxyalnusan*-5ξ-*ol* (300 mg) as needles, m.p. 266–268°, $[\alpha]_D \pm 0°$ (Found: C, 75·1; H, 10·5. $C_{34}H_{56}O_5$ requires C, 74·95; H, 10·4 per cent). It does not show selective absorption between 2000 and 3000 Å. Infra-red absorption (in Nujol): Bands at 1730, 1230 (acetate), 3570, 1033 and 970 cm^{-1} (hydroxyl). It does not give a colour with tetranitromethane in chloroform.

The triol diacetate (85 mg) in acetic acid (50 cm³) was treated at room temperature

* Specific rotations are for 1–2 per cent solutions in chloroform at 15 ± 5°. A light petroleum fraction, b.p. 60–80° and Grade II alumina were used for chromatography.

[8] A. Eschenmoser, L. Ruzicka, O. Jeger and D. Arigoni *Helv. Chim. Acta* **38**, 1890 (1955).

with chromium trioxide (1·2 mole) in acetic acid (10 cm³), added with stirring during 10 min, and the mixture kept at room temperature for 18 hr. The triol diacetate (60 mg) was recovered as needles from chloroform–methanol, m.p. and mixed m.p. 265–268°, $[\alpha]_D + 1°$.

Conversion of alnusene (V) *into olean*-13(18)-*ene* (VI) *and* 18α-*olean*-12-*ene* (VII). A solution of alnusene[3,4] (m.p. 181°, $[\alpha]_D + 56°$) (205 mg) in acetic acid (250 cm³) containing concentrated hydrochloric acid (60 cm³) was refluxed for 20 hr. Crystallisations of the product from chloroform–methanol gave the mixture of olean-13(18)-ene and 18α-olean-12-ene (100 mg) as blades m.p. 185–186°, $[\alpha]_D - 19°$, $- 18·5°$, undepressed in m.p. when mixed with a specimen (m.p. 186–187°, $[\alpha]_D - 18°$) prepared by the same acid treatment of olean-12-ene. The infra-red absorption spectra of the two specimens are identical.

Alnusa-1(10):5-*dien*-3α-*yl acetate* (IX, R = Ac). Selenium dioxide (1 g) in acetic acid (96 per cent, 26 cm³) was added to a solution of alnusenyl acetate (1 g) in glacial acetic acid (250 cm³), and the mixture kept at 60–70° for 1 hr. A solution of the product, obtained in the usual way, in light petroleum (60 cm³) was chromatographed on alumina (30 g). Light petroleum (600 cm³) eluted fractions which crystallised from chloroform–methanol to give alnusa-1(10):5-dien-3α-yl acetate (650 mg) as needles, m.p. 164–166°, $[\alpha]_D + 35°$; λ_{max} 2300 and 2380 Å (ε = 16,000 and 18,000), inflection at 2480 Å (ε = 11,000) (Found: C, 82·2, H, 11·0. Calc. for $C_{32}H_{50}O_2$: C, 82·3; H, 10·8 per cent). It gives a brown colour with tetranitromethane. Chapon[4] gives m.p. 163°, $[\alpha] + 33°$.

Alnusa-1(10):5-*dien*-3α-*ol* (IX, R = H). A solution of alnusadienyl acetate (250 mg) in ether (50 cm³) was refluxed with lithium alumium hydride (300 mg) for 20 min. Working up in the usual manner gave *alnusa*-1(10):5-*dien*-3α-*ol* (210 mg) which separates from chloroform–methanol as needles; m.p. 195–197°, $[\alpha]_D + 83°$, λ_{max} 2320 and 2390 Å (ε = 14,500 and 17,000), inflection at 2480 Å (ε = 11,000) (Found: C, 85·2; H, 11·7. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4 per cent). It gives a brown colour with tetranitromethane in chloroform.

Catalytic reduction of alnusa-1(10):5-*dien*-3α-*yl acetate*. (a) Alnusadienyl acetate (205 mg) in a mixture of *cyclo*hexane (45 cm³) and aqueous acetic acid (33 per cent w/w 20 cm³) was shaken with hydrogen and platinum (from 200 mg PtO_2) for 6 hr. Crystallisation of the product from chloroform–methanol gave alnus-5-en-3α-yl acetate (120 mg) as needles, m.p. and mixed m.p. 232–235°, $[\alpha]_D + 46°$. (b) A solution of alnusadienyl acetate (208 mg) in glacial acetic acid (150 cm³) was shaken with hydrogen and platinum (from 200 mg PtO_2) for 2½ hr. The product crystallised from chloroform–methanol to give alnusanyl acetate (135 mg) as small plates, m.p. and mixed m.p. 261–263°, $[\alpha]_D + 10°$, $+ 11°$.

Enol acetate from alnusenone. Concentrated sulphuric acid (1 drop) was added to a solution of alnusenone (160 mg) in *iso*propenyl acetate (25 cm³) and the mixture refluxed in nitrogen for 7 hr, with occasional removal of the condenser. Sodium acetate was added and the solvent removed. A solution of the product, isolated by means of ether, in benzene–light-petroleum (1 : 1; 30 cm³) was chromatographed on alumina (5 g). Benzene–light-petroleum (1 : 1; 200 cm³) eluted fractions which crystallised from chloroform–methanol to give the *alnusa*-2:5-*dien*-3-*yl acetate* (IV) (110 mg) as plates, m.p. 254–257°, $[\alpha]_D + 41°$, $\varepsilon_{2060} = 5800$ (Found: C, 82·2; H, 10·8. $C_{32}H_{50}O_2$ requires C, 82·3; H, 10·8 per cent). It gives a yellow colour with

tetranitromethane in chloroform. The enol acetate was hydrolysed by refluxing its solution in 5 per cent methanolic potassium hydroxide for 1½ hr. Crystallisation of the product from chloroform–methanol gave alnusenone as plates, m.p. and mixed m.p. 243–245°, $[\alpha]_D + 33°$.

Pyrolysis of alnusenyl benzoate. Alnusenyl benzoate (m.p. 234–235°, $[\alpha]_D + 16°$; 500 mg) was heated at 290–300° for 3 hr in nitrogen. A solution of the product in light petroleum (30 cm³) was chromatographed on alumina (15 g). Light petroleum (400 cm³) eluted fractions which crystallised from chloroform–methanol to give *alnusa*-2:5-*diene* (110 mg) as blades, m.p. 182–184°, $[\alpha]_D + 53°$, + 52°, $\varepsilon_{2110} = 6{,}500$ (Found: C, 88·1; H, 12·2. $C_{30}H_{48}$ requires C, 88·2; H, 11·8 per cent). It gives a yellow colour with tetranitromethane in chloroform.

Oxidation of alnusa-1(10):5-*dien*-3α-*ol.* Alnusadienol (180 mg) in pyridine (10 cm³) was added to a slurry of chromium trioxide–pyridine complex (from 1 g CrO_3 and 10 cm³ pyridine) and the mixture kept at room temperature for 17 hr. The product was isolated using ether, and its solution in light petroleum (30 cm³) chromatographed on alumina (10 g). Benzene–light-petroleum (1 : 2; 100 cm³) eluted a fraction, crystallisation of which from methanol gave *alnusa*-1:5(10)-*diene*-3:6-*dione* (X) (50 mg) as pale yellow blades, m.p. 253–255°, $[\alpha]_D + 62°$, + 63°, λ_{max} 2180 and 3190 Å ($\varepsilon =$ 11,000 and 8,300) (Found: C, 82·5; H, 10·1; O, 7·3. $C_{30}H_{44}O_2$ requires C, 82·5; H, 10·2; O, 7·3 per cent). Alnusadienedione was unchanged (m.p. and mixed m.p. 252–255°, $[\alpha]_D + 62°$) after refluxing its solution in acetic acid with *o*-phenylenediamine and sodium acetate for 2 hr.

Alnus-5(10)-*en*-3-*one* (XI). A solution of alnusenone (m.p. 245–246°, $[\alpha]_D + 31°$; 1·0 g) in hot glacial acetic acid (500 cm³) was treated with concentrated hydrochloric acid (12 cm³) and the mixture heated on the steam-bath for 18 hr. The mixture was evaporated to dryness under reduced pressure and the residue crystallised from chloroform–methanol to give *alnus*-5(10)-*en*-3-*one* (650 mg) as plates, m.p. 250–252°, $[\alpha]_D - 90°$ (Found: C, 85·1; H, 11·3. Calc. for $C_{30}H_{48}O$: C, 84·8; H, 11·4 per cent). Chapon[4] gives m.p. 248°, $[\alpha]_D - 84°$, for "ketone-II" prepared from alnusenone by treatment with sulphuric–acetic acid mixture. Alnus-5(10)-en-3-one gives a yellow colour with tetranitromethane in chloroform and a pink colour in the Zimmermann test.

Alnus-5(10)-*en*-3ξ-*ol* (XVII, R = H). A suspension of alnus-5(10)-en-3-one (200 mg) in dry ether (50 cm³) was treated at room temperature with lithium aluminium hydride (100 mg). The product, isolated in the usual manner, was thrice crystallised from light petroleum (b.p. 60–80°) to give *alnus*-5(10)-*en*-3ξ-*ol* as needles, m.p. 241–242°, $[\alpha]_D - 42°$ (Found: C, 84·8; H, 12·5. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8 per cent). Chapon[4] gives m.p. 229–231°, $[\alpha]_D \pm 0°$ for "alcohol-II".

Alnus-5(10)-*en*-3ξ-*yl acetate* (XVII, R = Ac). (a) Acetylation of alnus-5(10)-en-3ξ-ol using acetic anhydride and pyridine at 100° for 30 min yielded *alnus*-5(10)-*en*-3ξ-*yl acetate*, separating from chloroform–methanol as plates, m.p. 290–293°, $[\alpha]_D - 27°$ (Found: C, 82·0, H, 11·4. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2 per cent). Chapon[4] gives m.p. 276–278°, $[\alpha]_D - 15°$ for the acetate of "alcohol-II". (b) A refluxing solution of alnus-5(10)-en-3-one (100 mg) in benzene (10 cm³) and ethanol (50 cm³) was treated portionwise during 15 min with sodium (2 g) and the mixture poured into water. The product was isolated using ether and acetylated with acetic anhydride and pyridine at 100° for 15 min. The acetylated product crystallised from

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chloroform–methanol to give alnus-5(10)-en-3ξ-yl acetate as plates, m.p. and mixed m.p. 290–292°, $[\alpha]_D$ — 28°.

A suspension of alnus-5(10)-en-3ξ-yl acetate (55 mg) in dry ether (25 cm³) was treated with lithium aluminium hydride (50 mg) and the mixture refluxed for 5 min. The product crystallised from light petroleum to give alnus-5(10)-en-3ξ-ol as fine needles, m.p. 244–245° (no depression), $[\alpha]_D$ — 42·5° (Found: C, 84·35; H, 11·5 per cent).

Alnusa-1:5(10)-*dien*-3-*one* (XII). A solution of alnus-5(10)-en-3-one (250 mg) in glacial acetic acid (125 cm³) at 30° was treated over 5 min with a solution of bromine (95 mg) in acetic acid (6 cm³). Hydrogen bromide was evolved and the solution gradually developed a light brown colour. After 5 min potassium acetate (3 g) was added, the colour immediately changing to bright yellow. The mixture was heated on the steam bath for 2 hr and evaporated under reduced pressure. The product was isolated by means of ether and its solution in light petroleum was chromatographed on a column of alumina (15 g). Elution with light petroleum (400 cm³) gave a fraction (38 mg) crystallisation of which from chloroform–methanol yielded unchanged alnus-5(10)-en-3-one, m.p. 240–244° (no depression). Elution of the column with light petroleum–benzene mixtures and with benzene yielded fractions (175 mg) of m.p.'s between 211–215° and 216–217°. These were combined and crystallised from chloroform–methanol to give *alnusa*-1:5(10)-*dien*-3-*one* (100 mg) as yellow plates, m.p. 216–217°, $[\alpha]_D$ — 30°, λ_{max} 2070 and 3220 Å (ε, 7000 and 5500) (Found: C, 85·4; H, 11·3. $C_{30}H_{46}O$ requires C, 85·2; H, 11·0 per cent). The yellow colour of a solution of the dienone in chloroform is intensified by the addition of tetranitromethane.

Enol acetate from alnusa-1:5(10)-*dien*-3-*one*. A solution of alnus a-1:5(10)-dien-3-one (50 mg) in *iso*propenyl acetate (20 cm³) containing concentrated sulphuric acid (1 drop) was refluxed under nitrogen for 6 hr. After the addition of potassium acetate the solution was evaporated under reduced pressure and the product isolated by means of ether. Crystallisation from chloroform–methanol gave 3-*acetoxyalnusa*-2:1(10):5-*triene* (XIII) (30 mg) as pale yellow plates, m.p. 218–222°, $[\alpha]_D$ + 246°, λ_{max} 2040 and 3160 Å (ε, 7500 and 9100) (Found: C, 83·1; H, 10·7. $C_{32}H_{48}O_2$ requires C, 82·7; H, 10·4 per cent). A solution of the enol acetate in chloroform gives with tetranitromethane a brown colour which quickly fades.

Alnus-5(10)-*ene* (XIV). A mixture of alnus-5(10)-en-3-one (180 mg), hydrazine hydrate (100 per cent; 2 cm³) and methanolic sodium methoxide (from 0·2 g sodium and 25 cm³ methanol) was kept at 180° in an autoclave for 18 hr. The product, isolated in the usual way, crystallised from chloroform–methanol to give alnus-5(10)-ene (110 mg) as blades, m.p. 224–226°, $[\alpha]_D$ — 40°. Chapon[4] gives m.p. 225°, $[\alpha]_D$ — 38°.

Conversion of alnus-5(10)-*ene into olean*-13(18)-*ene and* 18α-*olean*-12-*ene*. A solution of alnus-5(10)-ene (110 mg) in acetic acid (125 cm³) and concentrated hydrochloric acid (30 cm³) was refluxed for 18 hr. Crystallisation of the product from chloroform–methanol gave the mixture (50 mg) of olean-13(18)-ene and 18α-olean-12-ene as blades, m.p. and mixed m.p. 185–186°, $[\alpha]_D$ — 19·5°.

Conversion of 4-*bromofriedelin* (XVI) *into alnusenone and alnus*-5(10)-*en*-3-*one*. 4-Bromofriedelin[7] (m.p. 198–199°, $[\alpha]_D$ + 88°; 375 mg) in ether (150 cm³) was added to a solution of silver acetate (375 mg) in water (4 cm³) and acetic acid (190 cm³),

the mixture boiled until the vapour temperature was 110° and then refluxed for 20 min. The product crystallised from chloroform–methanol to give the mixed crystal of alnusenone and alnus-5(10)-en-3-one as plates (220 mg), m.p. 247–249°, $[\alpha]_D$ — 52°.

*Synthetic mixture of alnus-*5(10)*-en-*3*-one* (XI) *and alnusenone* (II). A mixture of alnus-5(10)-en-3-one (100 mg, m.p. 250–252°, $[\alpha]_D$ — 90°) alnusenone (50 mg, m.p. 245–246°, $[\alpha]_D$ + 31°) was crystallised from chloroform–methanol to give plates, m.p. 247–249°, $[\alpha]_D$ — 51°. Recrystallisation from the same solvent gave plates m.p. 247–249°, $[\alpha]_D$ — 51·5°, undepressed in m.p. when mixed with the specimen prepared from 4-bromofriedelin.

*Alnusenyl acetate and alnus-*5(10)*-enyl acetate from friedelin.* A solution of the mixture (220 mg) of alnusenone and alnus-5(10)-en-3-one (prepared from friedelin) in ether (30 cm^3) and benzene (25 cm^3) was refluxed with lithium aluminium hydride (220 mg) for 20 min, and the product treated with acetic anhydride and pyridine on the steam-bath for 1 hr. Crystallisation from chloroform-methanol gave alnus-5(10)-enyl acetate as plates (80 mg) m.p. and mixed m.p. 290–292°, $[\alpha]_D$ — 25°. Concentration of the mother liquors gave a mixture of plates and needles, which was washed on the filter with chloroform–methanol (1 : 1) until only plates remained. Concentration of the washings gave needles (50 mg) which crystallised from chloroform–methanol to give alnusenyl acetate as needles (30 mg), m.p. and mixed m.p. 233–236°, $[\alpha]_D$ + 44°. The infra-red absorption spectrum of this sample is identical with that of an authentic reference specimen of alnusenyl acetate.

Acknowledgements—We thank the Department of Scientific and Industrial Research for a Grant and the Colonial Products Council for a Maintainance Award (to J. L. S.).

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THE CONSTITUENTS OF *PHEBALIUM NUDUM* HOOK—I

THE BARK

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(*Received* 21 *October* 1957)

Abstract—By a systematic investigation of the extractives of the bark of *Phebalium nudum* Hook twenty-one compounds have been isolated. Seventeen have been identified as D-citronellal, geranial, neral, acetic, *iso*valeric, palmitic and cinnamic acids, *iso*eugenol, β-sitosterol, α-terpineol, dictamnine γ-fagarine, evolitrine, skimmianine, kokusaginine, 9-hydroxy-4-methoxyfurano(3,2-*g*)benzopyran-7-one, and ellagic acid. The remaining four substances were obtained in a crystalline state, but in insufficient quantity for complete investigation. Two are new and appear to be of the coumarin type; they have been named phebalin and phebalarin. A partial structure has been proposed for phebalarin. The other two are aliphatic. The presence of at least a further ten phenolic substances has been shown by paper chromatography.

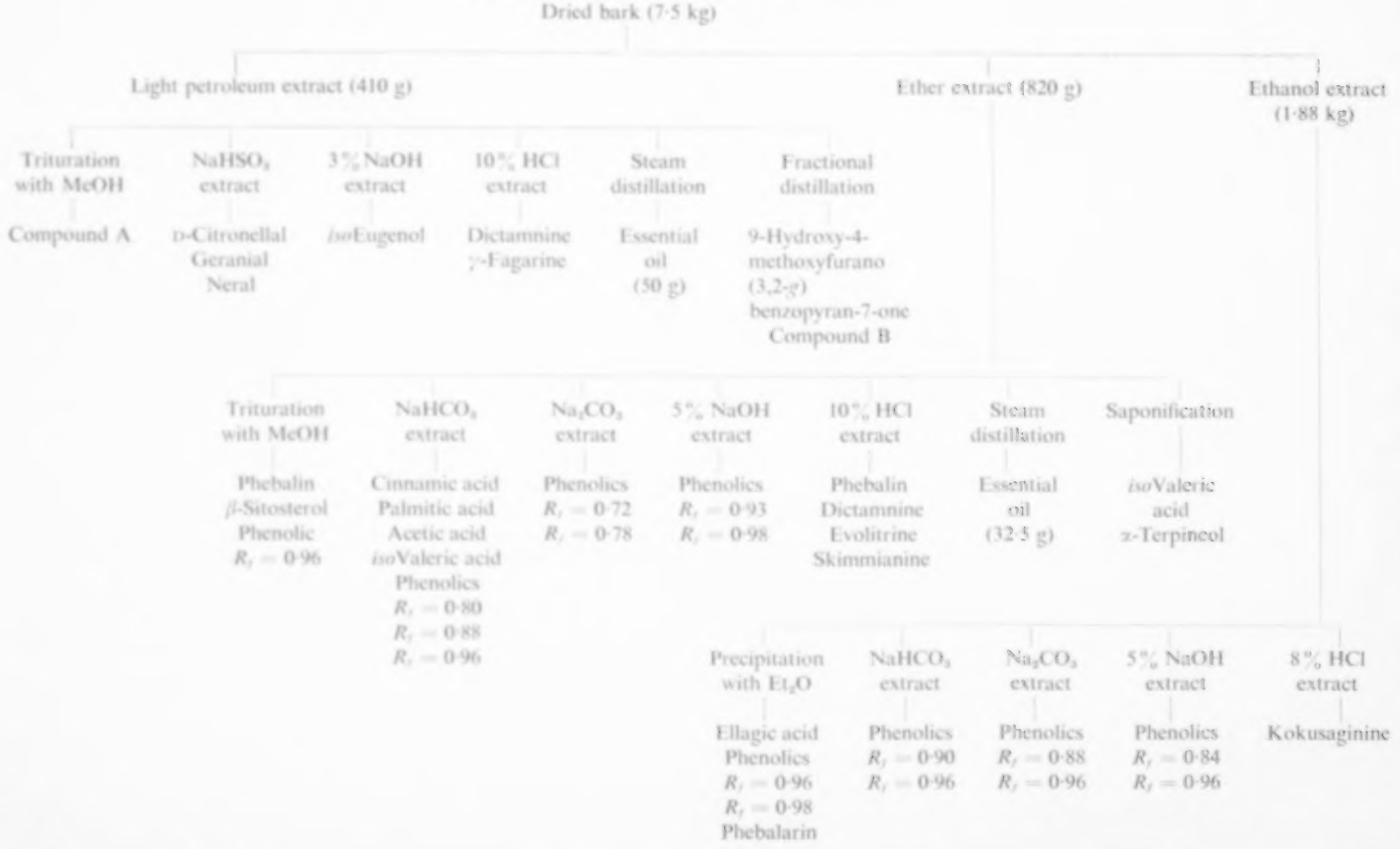
Phebalium nudum Hook (Maori name "Mairehau") is a shrub species of the Rutaceae and is the only member of the *Phebalium* genus found in New Zealand where it is endemic and confined to the northern part of the North Island. The leaves and bark possess a strong aromatic odour and the bark is coloured a pale yellow. The essential oil has been investigated by Radcliffe and Short[1] and found to contain citronellal, citral, acetic, *iso*valeric and cinnamic acids, an unidentified phenol, camphene, limonene, terpinyl acetate, and a mixture of unidentified sesquiterpenes.

The family Rutaceae is noted for its extremely diversified series of extractives, a common characteristic being the presence of methoxy and methylenedioxy groups, but seldom free phenolic groups. In view of the strong alkaloidal tests shown by the bark it was expected that the alkaloids present would be of the type related to anthranilic acid and particularly those isolated from Australian species.[2] Preliminary investigation on aliquot samples indicated that the alkaloids represented only a minor fraction of the total extracts. They could be isolated by acid extraction of the initial solvent extracts but precipitation as the picrates always gave products contaminated with large amounts of acid soluble tars. If the acidic and phenolic constituents were first removed by alkaline extraction, residues were obtained which on subsequent acid treatment, although giving fractions heavily contaminated with impurities, did lead to tractable products. Only in the case of the methanol extract were water soluble alkaloids observed by the usual test reagents, and these products represented but a minute quantity of the total alkaloidal content. A comprehensive investigation of the total extractives was therefore commenced, based on these preliminary investigations. The constituents and the extraction and fractionation scheme are summarised in Table 1.

Successive extraction with light petroleum, ether and ethanol gave a total extractive yield of 41·5 per cent of the dried bark, a considerable quantity of this consisting of phlobaphenic material. Both the light petroleum and ether extracts were mainly composed of oily products, difficult to separate and difficult to remove from solid products isolated. A complete investigation of the extractives would

[1] C. B. Radcliffe and W. F. Short *J. Soc. Chem. Industr., Lond.* **47**, 324T (1928).
[2] J. R. Price *Progress in the Chemistry of Organic Natural Products* Vol. XIII, pp. 302–345. Springer Publishing House, Austria (1956).

TABLE 1. *Phebalium nudum* BARK EXTRACTIVES



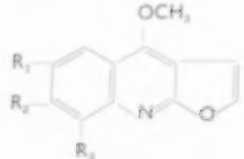
therefore entail techniques for the examination of an essential oil. Such an investigation was not attempted in the present work, attention being directed to the isolation and characterisation of the alkaloids and solid products present. By testing the products of the fractionation scheme with Mayer's and Dragendorff's reagents the location of the alkaloidal material could be determined during each step.

Trituration of the light-petroleum extract (5·47 per cent yield) with methanol gave a colourless neutral product, compound A, $C_{23}H_{44}O$, m.p. 81·5–82°, purified by crystallisation and chromatography. The infra-red spectrum showed strong bands at 1736 cm^{-1} (carbonyl) and 2924 cm^{-1} (CH_2). The substance, however, showed no unsaturation and gave no carbonyl derivatives. From these results it appears to be a monocyclic hydrocarbon possessing a sterically hindered oxo grouping. There was insufficient material for further investigation.

The aldehydes in the residual oil were extracted from their ethereal solution with aqueous sodium bisulphite and regenerated with sodium carbonate. The free aldehydes were separated by fractional distillation *in vacuo* and were identified as D-citronellal and citral. The semicarbazone of citral was further separated into geranial semicarbazone (major portion) and neral semicarbazone by fractional crystallisation from alcohol.[3] They could also be separated by the solubility of neral semicarbazone in ether, geranial semicarbazone remaining undissolved.[4]

Trial extractions of the ethereal solution, free from aldehydes, with saturated sodium hydrogen carbonate and 10% sodium carbonate solutions gave no products. These extracts were therefore omitted from the major fractionation scheme. Extraction with 3% sodium hydroxide gave no major solid products but ferric chloride tests indicated the presence of phenolic compounds. Solid derivatives were not obtained from the oily fraction by attempted purification by preparation of acetates, 3:5-dinitrobenzoates or chloracetic acid derivatives. Fractional distillation *in vacuo* however, gave as the major product, *iso*eugenol, purified by refractionation. The identity was confirmed by paper chromatography, the infra-red spectrum,[5] and by comparison of the 3:5-dinitrobenzoate with an authentic sample. A further yield was also obtained by steam-distillation of the crude oil.

The alkaloids were completely extracted from the ether solution with 10% hydrochloric acid and isolated by basification. The crude precipitate was separated by repeated fractional crystallisation from ethyl acetate–light petroleum into a crystalline alkaloid and a more soluble product. The crystalline alkaloid, further purified by chromatography, was identified as dictamnine, 4-methoxyfuro(2,3-*b*)quinoline[2] (I; $R_1 = R_2 = R_3 = H$) by circular paper chromatography in two solvent systems, the ultra-violet spectrum,[6] and by comparison of the free base with an authentic

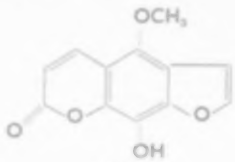


(I)

[3] E. Guenther *The Essential Oils* Vol. II, p. 326. Van Nostrand, New York (1948).
[4] E. S. Guenther and C. H. Grimm *J. Amer. Chem. Soc.* **60**, 933 (1938).
[5] L. Levi, J. L. Thompson, J. C. Evans, H. Bernstein, S. A. Forman and N. A. Miles *Proc. Sci. Sec., Toilet Goods Ass.* No. 25 (1956).
[6] J. Iriarte, F. A. Kincl, G. Rosenkranz and F. Sondheimer *J. Chem. Soc.* 4170 (1956).

sample. The more soluble alkaloid, γ-fagarine, 4:8-dimethoxyfuro(2,3-*b*)quinoline (I; $R_1 = R_2 = H$, $R_3 = OCH_3$), was isolated via the picrate and identified by comparison with an authentic sample.

A pale green essential oil (0·66 per cent yield), not further examined, was separated from the oil left after chemical fractionation, by steam-distillation. The residue was then fractionally distilled *in vacuo*, in twenty fractions which were stored at 0° for further investigation. The higher boiling fractions, after 3 months deposited a yellow phenolic substance, $C_{12}H_8O_5$, m.p. 222·5–223° identified by infra-red and ultra-violet



(II)

spectra and mixed m.p. as 9-hydroxy-4-methoxyfurano (3,2-*g*)benzopyran-7-one(II), recently found in the seeds of *Casimiroa edulis*.[7] To avoid confusion and to draw attention to the identity of the furanocoumarin with that isolated from *Casmiroa edulis* the name assigned by Rosenkranz *et al.*[7] has been adhered to for this compound. In the more usual system of naming it would be 8-hydroxy-5-methoxypsoralene.

Chromatography on alumina of the combined oil from the higher boiling fractions and the oil after separation of the furanocoumarin, gave a further neutral substance, compound B, $C_{13}H_{26}O$, m.p. 94°. It was not isolated in sufficient quantity for further investigation.

The brown viscous oil (10·93 per cent yield) obtained from the ether extract of the bark gave, on trituration with methanol and further purification, a crystalline compound, $C_{20}H_{18}O_4$, m.p. 175–176·5°. It contained one methoxyl group and from the infra-red[7] and ultra-violet[8] spectra appeared to be of the coumarin type. The compound is apparently new and has been named phebalin. Further structural studies are in progress. From an ether extract obtained during the purification of phebalin, β-sitosterol was isolated by chromatography on alumina. A phenolic impurity from this fraction was shown to be homogeneous by paper chromatography but was not obtained as a solid by chromatography on alumina.

The ether–alcohol solution remaining after trituration was fractionated between saturated sodium hydrogen carbonate, 10% sodium carbonate and 5% sodium hydroxide. The alkaloids were then removed by further extraction with 10% hydrochloric acid.

Cinnamic acid was isolated by crystallisation from a hot aqueous extract of the acidified sodium hydrogen carbonate fraction. From the aqueous phase after acidification three aliphatic acids were isolated by ether extraction and fractional distillation. The two acids boiling below 200° were identified as acetic and *iso*valeric acids and the higher boiling acid, obtained as a crystalline solid after chromatography, was identified as palmitic acid.

No solid material was obtained from the remaining phenolic fraction of the sodium hydrogen carbonate extract or the sodium carbonate and sodium hydroxide

[7] F. A. Kincl, J. Romo, G. Rosenkranz and F. Sondheimer *J. Chem. Soc.* 4163 (1956).
[8] W. L. Stanley and S. H. Vannier *J. Amer. Chem. Soc.* **79**, 3488 (1957).

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fractions by attempted acetylation. Each fraction behaved as a single substance when chromatographed on magnesia–celite or alumina. However, the presence of three phenolic substances in the sodium hydrogen carbonate fraction was indicated by paper chromatography. The other phenolic extracts each contained two substances. Forestal solvent[9] was used in all the paper chromatographic investigations. Bate-Smith[10] has shown that a large number of phenolic residues can be recognised using this solvent and that it is unequalled for general purposes. By using diazo spray reagents he has shown that distinctive colours are given with particular constituents and that the most useful of such reagents was diazotised *p*-nitroaniline diluted with 2 N sodium acetate. Examination of the chromatographic strips under ultra-violet light further distinguishes coumarin compounds by their blue-fluorescing properties from the more common phenolic constituents e.g. sinapic and ferulic acids. Bate-Smith[10] has shown further, that many members of the Rutaceae give complicated patterns of blue-fluorescing constituents, few of which have been identified. All the fractions from *Phebalium nudum* Hook, examined by these methods showed phenolic constituents with high R_f values, suggesting compounds of high complexity. Blue-fluorescing coumarin derivatives were absent in all cases when strips were examined with ammonia vapour.

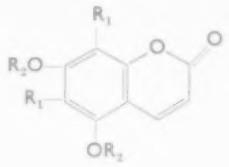
The alkaloids of the ether extract were completely contained in the 10% hydrochloric acid fraction. Dictamnine was again the principal alkaloid. By fractional crystallisation of the crude precipitate obtained on basification, a small yield of a crystalline furoquinoline alkaloid was isolated, identified by analysis of the picrate, m.p. and ultra-violet spectrum as evolitrine, 7-methoxyfuro(2,3-*b*)quinoline[2] (I; $R_1 = R_3 = H$, $R_2 = OCH_3$) previously only isolated in low yield from *Evodia littoralis*.[11] Dictamnine, evolitrine and phebalin (product of mechanical carry-over) were isolated from the mother-liquors of the fractional crystallisation by chromatography on alumina. A further furoquinoline alkaloid was isolated by ether extraction of the basified aqueous extract and precipitation as the crude picrate. The major product, after regeneration of the base by chromatography on alumina, was skimmianine, 4:7:8-trimethoxyfuro(2,3-*b*)quinoline[2] (I; $R_1 = H$, $R_2 = R_3 = OCH_3$), identified by comparison with an authentic sample.

The dark viscous oil remaining after fractionation was further separated into a steam-volatile essential oil (0·43 per cent) and a larger non-volatile fraction. Solid products were not isolated from the latter fraction by chromatography. Saponification followed by chromatography however, gave α-terpineol from the initial fractions. The major acid after saponification was *iso*valeric acid.

An aliquot of the ethanol extract (25·07 per cent yield) was dissolved in ethanol and the more insoluble constituents precipitated by the addition of ether. The material remaining in solution was then fractionated in a similar manner to that of the ether extract of the bark. The precipitated solid was dissolved in ethanol and a further phenolic fraction (two spots on chromatographic investigation) separated by the addition of water. Attempts to isolate traces of water soluble alkaloids from the aqueous ethanol solution by extended chloroform extraction were unsuccessful. However, fractionation of the residue after removal of the solvent gave a yellow

[9] E. C. Bate-Smith *Biochem. J.* **58**, 122 (1954).
[10] E. C. Bate-Smith *Sci. Proc. R. Dublin Soc.* **27**, 165 (1956).
[11] R. G. Cooke and H. F. Haynes *J. Aust. Chem.* **7**, 273 (1954).

crystalline coumarin, m.p. 125–126°, which possessed a free phenolic grouping. Analysis gave the formula $C_{15}H_{18}O_6$, and the ultra-violet spectrum was very similar to that of 5-geranyloxy-7-methoxycoumarin and 5:7-dimethoxycoumarin[8] suggesting that it is a 5:7-dialkoxycoumarin. A band in the infra-red at 3546 cm^{-1} was due to free hydroxyl stretching and bands assignable to tertiary hydroxyl deformations appeared at 1157, 1399, 1385, and 1337 cm^{-1}. The compound does not correspond to any naturally occurring coumarin[12] and has been named phebalarin. The partial structure III (R_1 = H or OH; R_2 = CH_3 or $CH_2{\cdot}CH_2{\cdot}C(OH){\cdot}(CH_3)_2$) is proposed from the available information.



(III)

The second fraction from this residue gave a positive Greissmayer test[13] and was shown to be composed mainly of ellagic acid[12] by paper chromatography. Bate-Smith[14] has shown that ellagic acid can be recognised instantly by inspection of a chromatogram in Forestal solvent.

The sodium hydrogen carbonate, sodium carbonate and sodium hydroxide fractions each contained two phenolic substances, one of which was common to each fraction. Their presence was demonstrated by paper chromatographic investigation in the usual manner.

The alkaloids contained in the ethanol extract were isolated as the picrates. The major picrate analysed for a trimethoxyfuroquinoline derivative, and the free base, on regeneration, was identified as kokusaginine, 4:6:7-trimethoxyfuro(2,3-*b*)quinoline[2] (I; R_3 = H, R_1 = R_2 = OCH_3), by comparison with an authentic sample. Fractionation of the ethanol extract with more concentrated acid gave only a trace of alkaloidal material.

EXPERIMENTAL

Microanalyses were by Dr. A. D. Campbell, University of Otago, N.Z. Infra-red spectra were measured as KBr discs, unless otherwise stated, with a Beckmann IR2 instrument. Ultra-violet spectra were measured for EtOH solutions with a Beckmann DU instrument. Light petroleum was of b.p. 60–70°.

Extraction of the bark. The finely ground bark of *Phebalium nudum* Hook, (7·5 kg, dried and stored for 4 years) was successively extracted (Soxhlet) with light petroleum, ether and ethanol, each extraction taking 32 hr with 8 gal of solvent. The bark was air-dried before successive extractions. The extracts were concentrated and the solvent removed by distillation under reduced pressure. No crystalline or solid material separated on successive concentration to half volume followed by cooling overnight. The concentrates of each extract gave positive Mayer's and Dragendorff's tests for alkaloids.

[12] F. M. Dean *Progress in the Chemistry of Organic Natural Products* Vol. IX, pp. 225–291. Springer Publishing House, Austria (1952).
[13] A. G. Perkin and M. Nierenstein *J. Chem. Soc.* **87**, 1412 (1905).
[14] E. C. Bate-Smith *Chem. & Ind. (Rev.) B.I.F. Rev.* R 32 (1956).

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Petroleum ether extract

Compound A. The dark green, viscous concentrate (410 g) was triturated with methanol (2·5 l.) and the green waxy solid separated and washed well with methanol. Precipitation with methanol from light petroleum gave a colourless, amorphous solid (1·25 g), m.p. 75–79°.* Successive crystallisation from light petroleum containing a few drops of benzene, ligroin, and twice from ethyl acetate, raised the m.p. to 78·5–80°.* Final purification by chromatography in light petroleum on alumina gave, as the major fraction, colourless plates (880 mg) of *compound A*, m.p. 81·5–82°, not raised on further crystallisation from ethyl acetate (Found: C, 82·2; H, 13·0. $C_{23}H_{44}O$ requires C, 82·1; H, 13·2 per cent). I.R.: 2924, 2890†, 1736, 1704, 1468, 1422, 1403, 1377, 1202†, 1185, 1182, 1121, 959, 922, 732, and 723 cm^{-1}.

The substance was soluble in light petroleum, ligroin, benzene, *cyclo*hexane, chloroform, carbon tetrachloride, dioxan and ethyl acetate. It was slightly soluble in ether and soluble in hot but not in cold alcohol, acetone, and acetic acid. It was insoluble in water and alkalies. With hot sulphuric acid it gave a reddish-brown coloration. It gave negative tests for unsaturation and the carbonyl group.

Citronellal and citral. Most of the solvent was removed from the combined filtrate and methanol washings of compound A. The green, oily concentrate (406 g) was taken up in ether (800 cm^3) and extracted with 35% aqueous sodium bisulphite containing free acetic acid (5 × 750 cm^3). The free aldehydes (8·3 g) were regenerated from the bisulphite derivatives (39 g) and from the aqueous layer, by the addition of 10% sodium carbonate (500 cm^3) and isolated by ether extraction. They possessed a strong lemon-like odour. Fractional distillation under reduced pressure gave two main fractions:

(a) B.P. 70–95°/10 mm, which gave citronellal (2·2 g), b.p. 200–210°, after refractionation. The semicarbazone crystallised as colourless plates from chloroform–ligroin, m.p. and mixed m.p. 82–83°. The 2:4-dinitrophenylhydrazone crystallised as yellow plates from methanol, m.p. and mixed m.p. 76–77°.

(b) B.P. 100–115°/10 mm, which gave citral (3·7 g), b.p. 225–230°, after refractionation. The 2:4-dinitrophenylhydrazone crystallised as orange-red needles from ethanol, m.p. 115–116°, undepressed on admixture with an authentic sample prepared from commercial citral. Fractional crystallisation of the semicarbazone, m.p. 132–135°, from methanol gave, as the major portion, needles of geranial semicarbazone, m.p. and mixed m.p. 163–164°. The minor portion, neral semicarbazone, crystallised from aqueous methanol as leaflets, m.p. and mixed m.p. 169–170°. Separation was also achieved by partial solution of citral semicarbazone in hot ether, geranial semicarbazone being insoluble.

iso*Eugenol.* The phenolic constituents were extracted from the ether solution with 3% sodium hydroxide (6 × 750 cm^3). Acidification of the extract gave a dark upper layer, separated by the addition of ether (50 cm^3). A further yield (320 mg) of a colourless material separated from the ether solution on standing. This product after crystallisation from ethyl acetate had m.p. 82–83°, undepressed by admixture with compound A, obtained above. Concentration of the ether solution, together with the ether extracts (3 × 200 cm^3) of the aqueous layer, under reduced pressure, after washing with water until the washings were neutral, gave a viscous amber oil (40·0 g).

* Melting points taken in evacuated tubes.
† Inflexion.

Steam-distillation for 10 hr and ether extraction of the distillate, gave a brown viscous oil (3·0 g). The infra-red spectrum and the chromatographic behaviour were identical with those of *iso*eugenol (see below). Fractional distillation of the residual crude oil *in vacuo* gave, as the major product, a fraction, b.p. 110–140°/10 mm, which on refractionation yielded *iso*eugenol (15 g), b.p. 266–269°. It gave a transient greenish-blue colour with alcoholic ferric chloride. Paper chromatography in Forestal solvent[9] (glacial acetic acid: concentrated hydrochloric acid: water (30 : 3 : 10 vol.) by the ascending method showed a single spot, $R_f = 0{\cdot}89$ (average of 6 determinations), in the same position as *iso*eugenol run as control. The spots were coloured orange in the presence of ammonia and brown with diazotised *p*-nitroaniline spray reagent.[10] The infra-red spectrum (contact film) was identical with that recorded by Levi and Thompson *et al.*[5] The 3:5-dinitrobenzoate, prepared in pyridine and crystallised twice from *n*-butanol, gave rosettes of long colourless needles, m.p. and mixed m.p. 156°.

Dictamnine. The ether solution was washed with concentrated brine (3 × 400 cm³) and with water (4 × 400 cm³) until the washings were neutral. Concentration under reduced pressure after drying, gave a dark green mobile oil (320 g) which gave strong positive alkaloid tests. The total alkaloid content was extracted with cold 10% hydrochloric acid after the addition of ether (50 cm³) and isolated by basification with aqueous ammonia. Repeated fractional crystallisation of the crude brown gummy precipitate (3·5 g) from ethyl acetate–light petroleum gave, as the more insoluble fraction, colourless needles of dictamnine (total yield 1·06 g), m.p. 129–130°. A sample chromatographed in benzene on alumina and eluted with benzene–ether (9 : 1), had m.p. 131–132°, unchanged on further recrystallisation from ethyl acetate–light petroleum and undepressed on admixture with an authentic sample (Found: C, 72·5; H, 4·5; N, 7·3, 6·9; OMe, 13·6, 13·2; NMe, nil. Calc. for $C_{12}H_9O_2N$: C, 72·35; H, 4·55; N 7·05; 1 OMe, 15·6 per cent). I.R. (identical with authentic dictamnine): 3175, 2985, 1621, 1580, 1543, 1506, 1466, 1449, 1416, 1385, 1366, 1340, 1297, 1266, 1235, 1209, 1179, 1160, 1121, 1088, 1052, 979, 940, 873, 791, 758, and 722 cm^{-1}. U.V.: λ_{max} 236 mμ (log ε 4·78), 309 mμ (log ε 3·95) and 329 mμ (log ε 3·88).

Circular paper chromatography of purified dictamnine showed a single band which had R_f values, 0·94 (BuOH: 2 N HCl) and 0·89 (BuOH: 5% HAc) (in reference 11 $R_f = 0{\cdot}89$). The bands were coloured orange with a modified Dragendorff's reagent spray, prepared by suspending bismuth oxychloride (2·61 g) and potassium iodide (10 g) in water (10 cm³) and adding 10% hydrochloric acid (6 cm³) with shaking.

Dictamnine picrate separated from methanol as light yellow plates, m.p. 164–165° (in reference 6 m.p. 165–166°) (Found: C, 50·75; H, 2·8. Calc. for $C_{12}H_9O_2N$, $C_6H_3O_7N_3$: C, 50·45; H, 2·85 per cent).

γ-Fagarine. The more soluble alkaloid fraction was isolated by precipitation as the crude picrate (780 mg), m.p. 165–171°. Repeated crystallisation from ethanol gave, as the major fraction, pale yellow needles of γ-fagarine picrate, m.p. 177–178°, with softening at 170–171°. (In reference 15 m.p. 177°) (Found: C, 50·9; H, 3·1; N, 12·2; OMe, 13·2; NMe, nil. Calc. for $C_{13}H_{11}O_3N$, $C_6H_3O_7N_3$: C, 49·8; H, 3·1; N, 12·2; 2 OMe, 13·5 per cent).

† Inflexion

[15] V. Deulofeu, R. Labriola and J. de Langhe *J. Amer. Chem. Soc.* **64**, 2326 (1942).

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The alkaloid was regenerated from the purified picrate with dilute aqueous lithium hydroxide. Two recrystallisations from ethyl acetate–ether gave small yellow needles of γ-fagarine, m.p. and mixed m.p. 140–141° I.R. (identical with authentic γ-fagarine): 3175, 2976, 2874†, 1515, 1460, 1395, 1381, 1337†, 1304, 1261, 1238†, 1189, 1159, 1094, 1053†, 908, 868, 816, 771, 751, and 726 cm^{-1}. U.V.: λ_{max} 238 mμ (log ε 4·76), 370 mμ (log ε 3·89) and 332 mμ (log ε 3·88). The hydrochloride crystallised as colourless needles from chloroform–ether, m.p. 158–159°. It decomposed when dried at 85°/P_2O_5/vac. for analysis.

Steam-volatile neutral oil. The ether solution was washed well with water (4 × 400 cm^3) until the washings were neutral and the solvent removed after drying. The dark green mobile oil (298 g) was then steam-distilled for 32 hr after addition of sodium chloride. The steam-volatile fraction was separated by addition of ether (20 cm^3) and by ether extraction (2 × 100 cm^3) of the aqueous distillate after saturation with sodium chloride. Removal of the solvent, under reduced pressure, from the dried solution, gave a pale green essential oil (50 g). It possessed the characteristic aromatic odour of the dried bark and had d_4^{25} 0·9949, n_D^{25} 1·5040, and $[\alpha]_D^{25}$ + 3·6° (l = 1, c = 1·95 in $CHCl_3$).

Non steam-volatile fraction. The volatile constituents of the residual oil (228 g) after steam-distillation, were separated by distillation *in vacuo* (100–350°/5 mm) after drying in ether solution. The dark brown distillate (162·3 g) had d_4^{25} 0·9982, n_D^{25} 1·6562, and $[\alpha]_D^{25}$ + 0·24° (l = 1, c = 5·38 in $CHCl_3$).

The oil was fractionally distilled; fractions 1–14, 115–252°/10 mm, fraction 15, 252–262°/10 mm, fractions 16–17, 230–300°/4 mm and fractions 18–20, 300–250°/1 mm.

9-*Hydroxy*-4-*methoxyfurano*(3,2-*g*) *benzopyran*-7-*one*. A yellow crystalline solid separated from fractions 15–17 on standing at 0° for 3 months. The compound (982 mg), m.p. 196–214°, was separated from adhering oil by washing with ether. It crystallised from ethanol as thick yellow rods, m.p. 221·5–222°, undepressed on admixture with an authentic sample of 9-hydroxy-4-methoxyfurano(3,2-*g*) benzopyran-7-one (Found: C, 62·1; H, 3·3; OMe, 13·0. Calc. for $C_{12}H_8O_5$: C, 62·1; H, 3·5; 1 OMe, 13·35 per cent). I.R.: 3390, 3175, 2976, 2874, 1709, 1647, 1613, 1595, 1484, 1451†, 1441, 1389, 1355, 1316, 1263, 1220, 1205, 1148, 1095, 1072, 1048, 1000, 962, 895, 871, 833, 808, 746 and 720 cm^{-1}. U.V.: λ_{max} 224 mμ (log ε 4·24), 272 mμ (log ε 4·28) and 316 mμ (log ε 4·03).

The furanocoumarin was readily soluble in 5% sodium hydroxide, with a yellow coloration which changed to purple on standing. Red and yellow colours were produced by concentrated sulphuric acid and ferric chloride respectively. The acetate, prepared by use of pyridine and acetic anhydride (1 hr, 90°), crystallised from methanol as colourless needles, m.p. 180–181° (in reference 7 m.p. 181–182°) (Found: C, 61·5; H, 3·4. Calc. for $C_{14}H_{10}O_6$: C, 61·3; H, 3·7 per cent).

Compound B. The combined oil from fractions 15–17 after separation of the furanocoumarin, and from fractions 18–20, was chromatographed in benzene on alumina columns. Elution with benzene and benzene–ether (9 : 1), gave greenish oils which on trituration with acetone deposited a colourless amorphous solid (187 mg) melting over a range, 50–60°. Crystallisation from methanol gave colourless, feathery needles of *compound B*, m.p. 94°,* with shrinking at 84° (Found, for sample dried at room temperature: C, 78·6; H, 12·9. $C_{13}H_{26}O$ requires C, 78·7; H, 13·2 per cent).

Solid products were not obtained by continued elution of the columns with ether and ether–methanol mixtures.

Ether extract

Phebalin. The brown viscous oil (820 g) from the ether extract was triturated with methanol (2·5 l.) and the solid separated. The deposit, after washing well with methanol and with light petroleum, consisted of a yellow amorphous material admixed with large, colourless, hexagonal crystals (15·2 g). Extraction with hot ether (A; 200 cm^3) left as residue the crystalline material (1·6 g), m.p. 158–161°. Repeated crystallisation from chloroform–methanol gave thick clusters of shining prismatic rods of *phebalin*, m.p. 171–172°, raised by chromatography in benzene–chloroform (9 : 1) on alumina to m.p. 175–176·5° (Found: C, 74·6, 74·55; H, 5·8, 5·8; OMe, 9·7, 9·6. $C_{20}H_{18}O_4$ requires C, 74·5; H, 5·6; 1 OMe, 9·65 per cent). I.R.: 3106, 2959, 2874†, 1730, 1603, 1560, 1497, 1458, 1437, 1404, 1397, 1340, 1284, 1253, 1182†, 1167, 1122, 1093, 1049, 1029, 994, 937, 891, 837, 803, 772 and 703 cm^{-1}. U.V.: λ_{max} 255 mμ (log ε 4·06) 285 mμ (log ε 4·15) and 322 mμ (log ε 4·29).

Phebalin was soluble in benzene, toluene, dioxan, dimethylformamide and chloroform. It was insoluble in water, light petroleum and ligroin and only slightly soluble in ether, ethyl acetate, alcohol and acetone. The compound was insoluble in hot 5% sodium hydroxide and insoluble in concentrated hydrochloric acid. With hot nitric acid it gave a yellow coloration and a yellow colour in cold concentrated sulphuric acid turning to dark red on warming. It gave a negative ferric chloride test, a negative cryptophenolic test[16] and a negative flavonoid test with magnesium and concentrated hydrochloric acid. The Molisch test was negative as was also the Labat test for methylenedioxy groupings with both phloroglucinol and gallic acid. Phebalin showed negative unsaturation tests with 1% permanganate, bromine in chloroform or acetic acid and also with tetranitromethane.

β-Sitosterol. The hot ether extract (A) of the triturated solid obtained above, on slow cooling deposited a pale yellow oily micro-crystalline solid (6·03 g), m.p. 63·5–67°. Partial solution in hot methanol (50 cm^3) followed by decantation of the hot solution separated the major fraction from a brown gum (B; 2·0 g). The cream amorphous solid (4·03 g), m.p. 62–70°, obtained from the methanol solution was chromatographed in benzene on alumina columns. From the fractions eluted with benzene–ether (5 : 1) colourless feathery plates of β-sitosterol were obtained, m.p. 134°, which separated from methanol as plates, m.p. and mixed m.p. 136–137° (Found: C, 83·8; H, 12·1. Calc. for $C_{29}H_{50}O$: C, 84·0; H, 12·1 per cent). The acetate had m.p. and mixed m.p. 127–128°.

Chromatography of the residue (B) in ethyl acetate on alumina gave no useful results, gummy products being obtained from all fractions after elution with ethyl acetate, ethyl acetate–acetone (1 : 1), and acetone. Paper chromatographic investigation in Forestal solvent in the usual manner showed a single brown spot $R_f = 0{\cdot}96$ (brown-red with the usual spray-reagent).

Ether extract fractionation. Removal of the solvent from the ether–alcohol solution gave a brown viscous oil (804·5 g) which, when dissolved in ether (600 cm^3), was fractionated with saturated aqueous sodium hydrogen carbonate (8 × 800 cm^3), 10% sodium carbonate (10 × 800 cm^3), 5% sodium hydroxide (10 × 800 cm^3) and

[16] L. Claisen *Liebigs Ann.* **418**, 69 (1919).

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10% hydrochloric acid (12 × 800 cm^3). The alkaline extractions were taken as complete when the last two extracts were colourless and the acid extract taken as complete when the last two extractions gave negative Mayer's tests. Only a trace of alkaloid material was obtained on further extraction with 20% hydrochloric acid, in insufficient quantity to isolate as picrate.

Cinnamic acid; phenolics. The acidified sodium hydrogen carbonate extract gave a brown oily upper layer which was separated by the addition of ether (50 cm^3). Removal of the solvent after washing with water (2 × 1 l.) and drying, gave a dark brown hygroscopic tar (33·4 g). Extraction of this fraction with hot water (2 × 250 cm^3) gave, on cooling, a crystalline acid (300 mg). Two recrystallisations from ethanol gave colourless plates of cinnamic acid, m.p. and mixed m.p. 132–132·5°.

The residual brown tar (32·68 g) after drying, gave no solid products on attempted purification by acetylation or by chromatography on a magnesia–celite (1 : 1) column; an apparently homogeneous brown band was obtained which showed no fluorescence under ultra-violet light. Chromatography in benzene on alumina showed the presence of two bands which on elution with benzene and benzene–ether mixtures, gave only gummy products.

Paper chromatographic investigation in Forestal solvent showed the presence of three phenolic compounds R_f = 0·80, 0·88 and 0·96, respectively (average of 3 determinations). Strips were run by the ascending method (cyanidin, control R_f = 0·50) and examined for spots with (a) ammonia vapour (b) ammonia vapour under ultra-violet light and (c) diazotised *p*-nitroaniline spray reagent. The spots were coloured blue-purple, orange, and red-brown, respectively with the spray reagent.

Acetic, isovaleric and palmitic acids. The aqueous layer, after acidification, was extracted with ether (2 × 2 l.) and the extract washed twice with water, dried, and the solvent removed. The brown viscous residue (17·7 g) possessed an unpleasant odour and, on fractional distillation, gave three main fractions;

(a) B.P. 106–120°/760 mm, which on refractionation gave acetic acid (9·1 g), b.p. 115–120°. The silver salt was prepared and analysed in the usual manner (Found: Ag, 64·3; equiv., 61·0. Calc. for $C_2H_3O_2Ag$: Ag, 64·6 per cent; equiv. = *M*, 60·0). The *s*-benzyl*iso*thiuronium salt separated as needles from dilute alcohol, m.p. and mixed m.p. 142–142·5°.

(b) B.P. 168–180°/760 mm, which on refractionation gave *iso*valeric acid (3·2 g), b.p. 175–179°. The silver salt was prepared and analysed in the usual manner. (Found: Ag, 51·9; equiv., 107. Calc. for $C_5H_9O_2Ag$: Ag, 51·7 per cent; equiv. = *M*, 102). The *s*-benzyl*iso*thiuronium salt separated as needles from dilute alcohol, m.p. and mixed m.p. 156–157°.

(c) B.P. 210–230°/10 mm. (2·68 g), which on chromatography in benzene on alumina and elution with the same solvent gave a pale yellow oil. Slow evaporation of the solvent left a discoloured waxy solid (30 mg), b.p. > 360, which on repeated crystallisation from benzene–methanol as waxy scales, had m.p. 60–63°, undepressed on admixture with palmitic acid. The acid was insoluble in water but readily soluble in sodium hydrogen carbonate. The anilide, prepared with ice-cold aniline via the acid chloride, and crystallised twice from alcohol and finally from benzene had m.p. 89–90°, undepressed by palmitanilide prepared in the same manner.

Ether extract; phenolics. The 10% sodium carbonate and 5% sodium hydroxide extracts on acidification, collection of the brown tarry precipitates and ether extraction

of the aqueous layer, gave in both cases, black sticky residues (9·73 g and 24·31 g, respectively), after washing, and drying in acetone solution. The extracts contained large quantities of phlobaphenic material. No crystalline products were isolated in attempted purification by acetylation or by chromatography on magnesia–celite (1 : 1) or alumina columns, apparently homogeneous brown bands being obtained in all cases.

Paper chromatographic investigation in Forestal solvent in the usual manner gave the following results: Na_2CO_3 extract, R_f 0·72 (orange) and 0·78 (orange); NaOH extract, R_f 0·93 (brown) and 0·98 (brown-red).

Evolitrine and skimmianine. The 10% hydrochloric acid extract was basified with aqueous ammonia and the gummy precipitate (4·43 g) isolated by filtration. Repeated fractional crystallisation from ethyl acetate and again from ethyl acetate–light petroleum gave two main fractions;

(a) Thick, colourless rods (274 mg), m.p. 164–168°, raised to m.p. 175–175·5° by three recrystallisations from chloroform–methanol. The substance was identified as phebalin by mixed m.p. and the infra-red spectrum. The product gave a negative qualitative test for nitrogen and had identical properties with those recorded earlier for phebalin.

(b) Rosettes of needles of evolitrine (22 mg), m.p. 114–115°, unchanged on further recrystallisation from light petroleum (in reference 11 m.p. 114–115°). U.V.: λ_{max} 247 mμ (log ε 4·84), 308 mμ (log ε 4·01), 320 mμ (log ε 3·98) and 333 mμ (log ε 3·90). The picrate crystallised from ethanol as pale yellow needles, m.p. 191–192° (in reference 11 m.p. 191–192°). Found: C, 49·8; H, 3·1; OMe, 14·0; NMe, nil. Calc. for $C_{13}H_{11}O_3N$, $C_6H_3O_7N_3$: C, 49·8; H, 3·1; 2 OMe, 13·5 per cent).

Chromatography of the gummy residue from the mother-liquors from fraction (b) above, in benzene on alumina, gave three major fractions;

(c) Colourless needles (150 mg), m.p. 127–128°, raised by further recrystallisation from ethyl acetate, to m.p. 131–132°, undepressed by dictamnine isolated from the light petroleum extract. The picrate formed yellow plates from methanol, m.p. and mixed m.p. 164–165°.

(d) Colourless needles (51 mg), m.p. 102–110°, raised by further recrystallisation from light petroleum to m.p. 114–115°, undepressed by evolitrine obtained from (b) above. The picrate formed yellow needles from ethanol, m.p. and mixed m.p. 191–192°.

(e) Colourless rods (40 mg), m.p. 162–165°, raised on repeated recrystallisation from ethyl acetate to m.p. 174–175°, undepressed by phebalin.

The basified aqueous solution was extracted with ether (5 × 2 l.). It then gave a negative alkaloid test. The brown oil (9·40 g) obtained from the ether extract after washing and drying and removal of the solvent, was taken up in ethanol (20 cm³) and treated with excess of hot ethanolic picric acid. The crude picrate mixture (1·84 g), m.p. 162–164° (decomp.), on extraction with hot ethanol (2 × 50 cm³) gave, as the major fraction, pale yellow needles (800 mg), m.p. 190–191·5°. Three recrystallisations from dioxan gave fine pale yellow needles of skimmianine picrate, m.p. and mixed m.p. 195–196° (Found: C, 49·4; H, 3·25; N, 11·5. Calc. for $C_{14}H_{13}O_4N$, $C_6H_3O_7N_3$: C, 49·2; H, 3·3; N, 11·5 per cent).

Regeneration of the base from the picrate by chromatography in ethyl acetate on alumina gave skimmianine, colourless prisms from aqueous ethanol, m.p. and mixed

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m.p. 177°. I.R. (identical with authentic skimmianine): 3175, 2976, 2874, 1623, 1580, 1550, 1508, 1497†, 1451, 1391, 1383, 1323, 1295, 1271, 1238, 1217, 1152, 1117†, 1094, 1058, 1043, 996, 987, 951, 888, 873, 826, 809, 776, and 741 cm^{-1}.

Steam-volatile neutral oil. The dark ether solution remaining after chemical fractionation was washed with water until the washings were neutral, dried, and the solvent removed. The dark viscous oil (122 g) was then steam-distilled for 36 hr after addition of sodium chloride. The steam-volatile fraction was separated by addition of ether (50 cm^3) and by ether extraction (2 × 2 l.) of the aqueous distillate after saturation with sodium chloride. Removal of the solvent under reduced pressure, from the dried solution, gave a dark green essential oil (32·5 g).

Non steam-volatile fraction. The residual oil (88·2 g) after steam-distillation was washed well with water, dried, and the volatile constituents (51·9 g), separated by distillation *in vacuo* (100–300°/10 mm). Considerable charring occurred above 300°. Preliminary chromatography in benzene on alumina gave no useful results. The oil was saponified in ethanol (30 cm^3), by refluxing with 2 N alcoholic KOH at 100° for 2 hr. Ethanol was removed by distillation under slightly reduced pressure in a slow stream of carbon dioxide, water (200 cm^3) added, and the mixture extracted with ether (2 × 200 cm^3). The black oil obtained on removal of the solvent from the dried extract was chromatographed in benzene on alumina. The initial fractions, eluted with the same solvent, gave α-terpineol as a brown oil (500 mg), b.p. 212–220°/760 mm. Treatment with dry hydrogen chloride in anhydrous ether solution and crystallisation from aqueous methanol gave colourless plates, m.p. 48·5–49°, undepressed by dipentene bis-hydrochloride prepared from α-terpineol in the same manner.

Acidification of the aqueous phase, after saponification and ether extraction gave, as the major fraction, *iso*valeric acid (500 mg), b.p. 174–179°. The *s*-benzyl-*iso*thiuronium salt had m.p. and mixed m.p. 156–157°.

Ethanol extract

Ethanol extract fractionation. The black sticky tar (1·88 kg) from the alcohol extract contained a large amount of phlobaphenic material and gave only weak alkaloid tests. An aliquot (910 g) was dissolved in hot ethanol (3 l.), and ether (7 l.) added to the cooled solution which was then allowed to stand at room temperature overnight. The solution was decanted from the thick syrupy deposit (A) and successively fractionated between saturated sodium hydrogen carbonate (3 × 2·75 l.), 10% sodium carbonate (3 + 2 l.), 8% hydrochloric acid (4 × 2 l.), 12% hydrochloric acid (2 × 2 l.), 20% hydrochloric acid (5 × 2 l.) and 36% hydrochloric acid (2 × 1·5 l.) in a similar manner to the ether extract.

The more ether–alcohol insoluble syrup A (213·5 g) was dissolved in ethanol (1 l.) and poured into water (6 l.). The washed and dried flocculent precipitate (35·6 g) contained a large amount of phlobaphenic material (9·76 g). Extraction of the dried deposit with hot acetone (4 × 100 cm^3) and with hot ethanol (3 × 100 cm^3), separated two further fractions. These extracts on removal of the solvent, gave brown resins (15·1 g) and (10·8 g), respectively, which could not be obtained in a crystalline state or purified by acetylation. Paper chromatographic investigation in the usual manner gave the following results; acetone soluble fraction, $R_f = 0{\cdot}96$ (red); ethanol soluble fraction $R_f = 0{\cdot}98$ (blue-brown).

Phebalarin. The brown gum (17·8 g), remaining after removal of the solvent from

the aqueous ethanol solution obtained from A, was treated with hot ethanol (B; 2 × 25 cm³).

The sparingly ethanol soluble residue (4·92 g), m.p. >360°, on further extraction with hot acetic acid (20 cm³) left phlobaphenic material (4·5 g). Addition of water (10 cm³) to the cooled solution deposited a pale yellow crystalline solid (373 mg), m.p. 116–118°. Recrystallisation from ethanol gave pale yellow needles of *phebalarin*, m.p. 125–126° (Found: C, 61·3; H, 6·1. $C_{15}H_{18}O_6$ requires C, 61·2; H, 6·2 per cent). I.R.: 3546, 2985, 1709, 1621, 1582, 1563, 1546, 1520, 1475†, 1460, 1425, 1399, 1385, 1337, 1256†, 1196†, 1157, 1117, 1034, 997†, 920, 841, and 795 cm⁻¹. U.V.: λ_{max} 225 mμ (log ε 4·24), 236 mμ (log ε 4·16), 245 mμ (log ε 4·18) and 332 mμ (log ε 4·25).

Phebalarin was insoluble in sodium hydrogen carbonate but dissolved in aqueous sodium carbonate with a strong yellow coloration. It gave a green colour with ferric chloride. The substance dissolved in concentrated sulphuric acid to give a yellow solution, changed on warming to a blue-green colour. The magnesium–hydrochloric acid test for flavonoids was negative.

Ellagic acid. The ethanol soluble fraction B, on slow evaporation deposited ellagic acid as a yellow microcrystalline powder (1·66 g), m.p. >360. The product gave a dark red colour with nitric acid containing nitrous acid, and, in methanol solution, gave a yellow colour with acetic acid and sodium nitrite,[14] changing to orange-brown on standing. Paper chromatographic investigation in Forestal solvent in the usual manner gave a single spot, $R_f = 0{\cdot}32$ (in reference 14 $R_f = 0{\cdot}33$). The spot was violet under ultra-violet light, yellow in the presence of ammonia/u.v. and red-brown when sprayed.

Phenolics. The sodium hydrogen carbonate, 10% sodium carbonate and 5% sodium hydroxide extracts on acidification all gave dark brown tarry precipitates, 59·6 g, 23·72 g, and 10·05 g, respectively. The extracts contained large quantities of phlobaphenic material. No crystalline products were isolated in attempted purification by chromatography on magnesia–celite (1 : 1) or alumina columns, apparently homogeneous, brown bands being obtained in all cases. Paper chromatographic investigation in Forestal solvent by the previous method gave the following results; $NaHCO_3$ extract, $R_f = 0{\cdot}90$ (orange), Na_2CO_3 extract, $R_f = 0{\cdot}88$ (blue); NaOH extract, $R_f = 0{\cdot}84$ (orange–red). Each extract gave a further spot $R_f = 0{\cdot}96$ (brown-red).

The aqueous filtrate after acidification of the sodium hydrogen carbonate fraction gave a faint positive Mayer's test for water soluble alkaloids. Although they could be separated from the basified solution by continuous extended chloroform extraction for 72 hr, the brown concentrate (15·8 g) retained a large quantity of gummy impurities. Further purification by extraction with 10% hydrochloric acid (4 × 250 cm³) from chloroform solution (50 cm³) followed by basification and chloroform extraction separated non-nitrogenous impurities. The crude alkaloid residue (2·3 g) still retained a large quantity of oily impurities. The alkaloids were not present in sufficient quantity for isolation as insoluble hydrochlorides or by precipitation as the picrates from alcoholic or chloroform solution.

Kokusaginine. The 8% hydrochloric acid extract was basified with ammonia with cooling, and the crude alkaloid gum (1·20 g) separated and washed well with water (the aqueous layer, and washings gave alkaloid tests). The gum was separated from black non-nitrogenous impurities (210 mg), by extraction with hot ether (4 × 25 cm³)

containing chloroform (5 cm^3) and the alkaloid content precipitated by treatment with excess of ethanolic picric acid. The crude picrate (833 mg), m.p. 184°, crystallised once from ethanol and twice from dioxan as large yellow needles, had m.p. 212–213°, undepressed on admixture with kokusaginine picrate (m.p. 217–218°) (Found: C, 49·3; H, 3·1; N, 11·5; OMe, 18·6. Calc. for $C_{14}H_{13}O_4N$, $C_6H_3O_7N_3$: C, 49·2; H, 3·3; N, 11·5; 3 OMe, 19·0 per cent.) Regeneration of the free base by chromatography in ethyl acetate on alumina gave kokusaginine, colourless prisms from benzene, m.p. and mixed m.p. 171°. I.R. (identical with authentic kokusaganine): 3125, 2941, 1623, 1585, 1543, 1506, 1479, 1458, 1418, 1395, 1360, 1318, 1312, 1253, 1208, 1167, 1155, 1138, 1089, 1046, 1008 988 945, 858, 840, 794, 771, and 744 cm^{-1}.

The 12, 20 and 36% hydrochloric acid extracts, on working up in the previous manner, contained only traces of alkaloidal material, in insufficient quantity to isolate picrates.

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MITTLERE RINGE—XIII*

DIE INTRAMOLEKULARE ACYLIERUNG DER ω-(1-NAPHTHYL)-FETTSÄUREN

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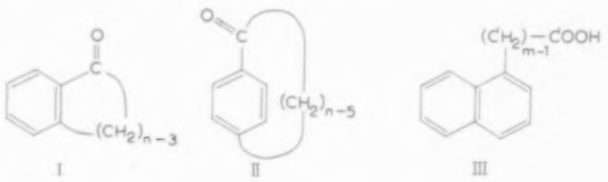
Zusammenfassung—Die intramolekulare Friedel–Crafts-Reaktion der ω-Aryl-fettsäuren in hoher Verdünnung, die sich in der Benzolreihe als wertvolles synthetisches Prinzip zur Darstellung von Ringketonen bewährt hat, wird auf die ω-(1-Naphthyl)-fettsäuren übertragen. Bis zur ε-(1-Naphthyl)-capronsäure werden die Ketonringe gemäss IV mit 5–8-gliedrigem Ring gebildet. Die höheren 1-Naphthyl-fettsäuren schliessen den Ring bevorzugt gegen die Position 7 zu VII als neuem Typ von heteronuclearen Ringketonen der Naphthalin-Reihe. Bei der ω-(1-Naphthyl)-decansäure tritt die 1,4-Verknüpfung in Konkurrenz zur 1,7-Annellierung auf.

Die durch die "Mittlere-Ring-Torsion" erzwungene sterische Mesomeriehinderung wird in den verschiedenen Klassen der Naphthocyclenone, vor allem anhand der Lichtabsorption, untersucht.

Abstract—The intramolecular Friedel–Crafts cyclisation of ω-arylalkanoic acids, which is in the benzene series a valuable synthetic route to bicyclic ketones with medium-sized and large rings, has been investigated with ω-(1-naphthyl)alkanoyl chlorides. The lower members, including naphthylcaproic acid, close the ring at position 2 to form IV. The higher homologous acids show a preference for annellation at 7, making available a new type of heteronuclear naphthalene cyclic ketones (VII). During cyclisation of ω-(1-naphthyl) decanoic acid, the 1,4 ring closure competes with the 1,7 type.

Steric hindrance of resonance as a consequence of "medium ring torsion" was studied in different classes of naphthocyclenones.

DIE intramolekulare Friedel–Crafts-Acylierung der ω-Phenyl-fettsäure-chloride *in hoher Verdünnung* eröffnete den Weg zu 1,2-Benzo-cyclen-(1)-onen-(3) (I) sowei 1,2,3,4,-Benzo-cycladien-(1,3)-onen-(5) (II) mit mittleren und grossen Ketonringen.[1–3] Die Übertragung dieses Syntheseprinzips auf die Naphthalinreihe erschien umso einladender als die hier erstmalig zugänglichen Ringketone erhebliches theoretisches Interesse beanspruchen. Insbesondere die sterische Mesomeriehinderung in mittleren Ringen war Gegenstand eingehender Untersuchungen.[3,4]



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[4] R. Huisgen, W. Rapp, I. Ugi, H. Walz und E. Mergenthaler *Liebigs Ann.* **586**, 1 (1954): vgl. auch Literatur 1 und 2.

(a) *Darstellung der ω-(1-Naphthyl)-fettsäuren*

Zur Einführung der Fettsäurekette in den Naphthalinkern eignet sich die Friedel–Crafts-Synthese mit Dicarbonsäure-anhydriden resp. -halbester-chloriden. Diese Acylierung führt zu Gemischen der isomeren 1- und 2-Naphthyl-Verbindungen, deren Zusammensetzung von den Reaktionsbedingungen, vor allem vom Solvens abhängt.[5] Während die unterschiedlichen Löslichkeiten eine Trennung der β-(1-Naphthoyl)- und β-(2-Naphthoyl)-propionsäuren erlauben,[6] bereitete die Isomerentrennung bei den Produkten der Acylierung mit höheren Dicarbonsäurehalbesterchloriden steigende Schwierigkeiten. Es gelang uns stets, die schwerer lösliche

TABELLE 1. DARSTELLUNG UND SCHMELZPUNKTE DER ω-(1-NAPHTHYL)-FETTSÄUREN (III)

III, m =	Schmp.	Synthese
3	156–157°	Naphthyl-1-methyl-chlorid + Malonester
4	108–109°	Naphthalin + Bernstein-halbester-chlorid
5	88,5–89°	3-(1-Naphthyl)-propyl-bromid + Malonester
6	78,6–79,2°	Naphthalin + Adipinester-chlorid oder 1-Naphthyl-Cd + Adipinesterchlorid
7	64,5–65°	3-(1-Naphthyl)-propyl-Cd + Bernsteinsäure-halbester-chlorid
8	58,0–58,8°	1-Naphthyl-Cd + Korksäure-halbester-chlorid
9	61,0–61,7°	1-Naphthyl-Cd + Azelainsäure-halbester-chlorid
10	71,8–72,4°	1-Naphthyl-Cd + Sebacinsäure-halbester-chlorid
16	68,5–69,0°	1-Naphthyl-Cd + Thapsiasäure-halbester-chlorid

2-Naphthoyl-Verbindung aus der Spitzenfraktion zu isolieren; für die Darstellung der ω-(1-Naphthoyl)-fettsäuren erwies sich dieser Weg als unrationell.

Elektrophile Substitutionen, die mit grossem Vorzug in der Naphthalin-1-Stellung stattfinden, sind die Chlormethylierung und Bromierung. Die Überführung des 1-Chlormethyl-naphthalins in die β-(1-Naphthyl)-propionsäure findet sich bereits beschrieben.[7] Jedoch schlugen unsere Bemühungen, die Seitenkette durch Umsatz des Di-(naphthyl-1-methyl)-cadmiums mit Dicarbonsäure-halbester-chloriden zu verlängern,[8] fehl. Schon die Grignardierung des Chlormethyl-naphthalins liess sich nicht befriedigend erzielen; 1:2-Di-(1-naphthyl)-äthan wurde unter den Produkten gefunden. Wohl konnte die leicht zugängliche Dreikohlenstoff-Seitenkette mittels Malonester-oder der eben erwähnten metallorganischen Synthese verlängert werden.

Glatt vollzog sich dagegen die Reaktion des aus 1-Bromnaphthalin bereiteten Di-(1-naphthyl)-cadmiums mit den Halbesterchloriden der Dicarbonsäuren mit 6, 8, 9, 10 und 16 C-Atomen. Formal entsprechen die erhaltenen Ketosäuren dem Ergebnis einer auf die 1-Position des Naphthalins beschränkten Friedel–Crafts-Acylierung.

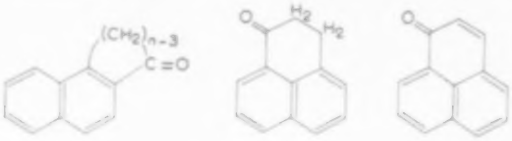
Nur die niederen ω-(1-Naphthyl)-fettsäuren liessen sich aus den Ketosäuren durch Clemmensen–Martin-Reduktion[9] bereiten; die Reduktion mit Zink in wässriger Essigsäure oder verd. Alkohol überwand zwar die durch die geringe Löslichkeit bedingten Schwierigkeiten, führte aber zu viel Nebenprodukten. Die Wolff–Kishner-Reduktion in der Huang-Minlonschen Arbeitsweise[10] erwies sich als

[5] G. Baddeley *J. Chem. Soc.* 99 (1949); weitere Literatur bei P. H. Gore *Chem. Rev.* **55**, 241 (1955).
[6] R. D. Haworth *J. Chem. Soc.* 1125 (1932).
[7] L. F. Fieser und M. D. Gates *J. Amer. Chem. Soc.* **62**, 2335 (1940).
[8] J. Cason *Chem. Rev.* **40**, 15 (1947); *Org. Synth.* **28**, 75 (1948).
[9] E. L. Martin *J. Amer. Chem. Soc.* **58**, 1438 (1936); *Org. React.* **1**, 155 (1942).
[10] Huang-Minlon *J. Amer. Chem. Soc.* **68**, 2487 (1946).

überlegen. Tabelle 1 vermittelt die übersicht der hier dargestellten ω-(1-Naphthyl)-fettsäuren (III), von denen sich nur die drei ersten Glieder in der Literatur beschrieben fanden.

(b) *Naphtho*-[1′,2′:1,2]-*cyclen*-(1)-*one*-(3)

Von den in der Überschrift genannten Ringketonen der Formel IV waren die Vertreter mit 5- und 6-gliedrigem Ring bereits bekannt. Bei der intramolekularen Cyclisierung der β-(1-Naphthyl)-propionsäure tritt die Bildung des Ketons IV, $n = 5$ hinter der des Perinaphthanons (V)[11] oder gar der des Dehydrierungsproduktes



IV V VI

VI zurück.[12] Günstiger ist der Weg über die β-(2-Napthoyl)-adrylsäure, die mit Aluminiumchlorid über die Carbonsäure das 4,5-Benzo-indanon (IV, $n = 5$) liefert.[13] Für den leichten Ringschluss der γ-(1-Naphthyl)-buttersäure zu IV, $n = 6$ stehen eine Fülle von Methoden zur Verfügung;[14] die Schliessung eines 7-gliedrigen Ringes über die peri-Positionen konkurriert nur noch, wenn eine Methoxylgruppe in 5 oder 7 lenkt.[15]

Zu den Naphtho-cyclenonen IV, $n = 7$ und 8 gelangten wir mittels Hochverdünnungs-Cyclisierung der Säurechloride mit Aluminiumchlorid in Schwefelkohlenstoff; mit Zutropfgeschwindigkeiten von 2,5 bezw. 1,0 mMol. Säurechlorid/Stde. erzielten wir Rohausbeuten von 96 bezw. 70% d.Th. am Keton mit 7- bezw. 8-gliedrigem Ring. Die konstitutionelle Sicherung der wohlkristallisierten Ketone IV, $n = 7$, 8 erfolgte über die Oxydation mit 40%-Salpetersäure zur Benzol-1,2,3,4-tetracarbonsäure. Die Ringketone IV, $n = 7$, 8 lieferten im Gegensatz zu $n = 5,6$ *geometrisch-isomere* 2,4-*Dinitrophenyl-hydrazone*. IV, $n = 9$ liess sich nicht mehr bereiten, da die intramolekulare Acylierung von III, $m = 7$ in einer anderen Stellung erfolgt (S. 276).

Die *UV-Spektren* der Naphtho-cyclenone IV zeugen von einer sehr ausgeprägten "Mittleren-Ring-Torsion."[16] Die Extinktion der Bande des $N \rightarrow V_1$-Übergangs des aromatischen Ketons bei 250 mμ zeigt die Wirksamkeit der Konjugation zwischen Carbonylgruppe und aromatischem Kern an. Schon beim Übergang von IV, $n = 5$, 6 zu $n = 7$ sinkt die Extinktion dieser Bande beachtlich. In IV, $n = 8$ führt die "Mittlere-Ring-Torsion" zu einem so starken Herausdrehen der Carbonylgruppe aus der Bindungsebene des Naphthalinsystems, dass nur noch eine Schulter bei 240–250 mμ die Koppelung der π-Systeme erkennen lässt (Abb. 1). Die *sterische Mesomeriehinderung* ist hier viel stärker ausgeprägt als in der 1:2-Benzo-cyclenon-(3)-Reihe I,[4]

[11] Die Cyclisierung der freien Carbonsäure mit HF gibt 81% V neben 6% IV, $n = 5$: L. F. Fieser und M. D. Gates *J. Amer. Chem. Soc.* **62**, 2335 (1940); M. F. Ansell *J. Chem. Soc.* 575 (1954); M. F. Ansell und A. M. Bermann *Ibid.* 575 (1954).

[12] F. Mayer und A. Sieglitz *Ber. Dtsch. Chem. Ges.* **55**, 1835 (1922); J. W. Cook und C. L. Hewett *J. Chem. Soc.* 365 (1934).

[13] G. Baddeley, G. Holt, S. M. Makar und M. G. Ivinson *J. Chem. Soc.* 3605 (1952).

[14] Übersicht bei W. S. Johnson *Org. React.* **II**, 114 (1944).

[15] G. A. R. Kon und H. R. Soper *J. Chem. Soc.* 790 (1939); R. C. Gilmore und W. J. Horton *J. Amer. Chem. Soc.* **72**, 733 (1950); A. L. Green und D. H. Hey *J. Chem. Soc.* 4306 (1954).

wo die Extinktion bei I, $n = 8$ nur auf knapp den halben Wert der koplanaren Verbindung I, $n = 6$ absinkt. Vermutlich führt die Wechselwirkung mit der Naphthalin-*peri*-Position zu einer Schubkraft,[3] welche über die Pressung der Wirkungsradien die Torsion zwischen der Carbonylgruppe und dem aromatischen Kern erhöht.[16] Die Banden der Kern-Anregung zwischen 260 und 350 mμ zeigen im mittleren Ringgebiet einen charakteristischen Verlust an Feinstruktur.[4]

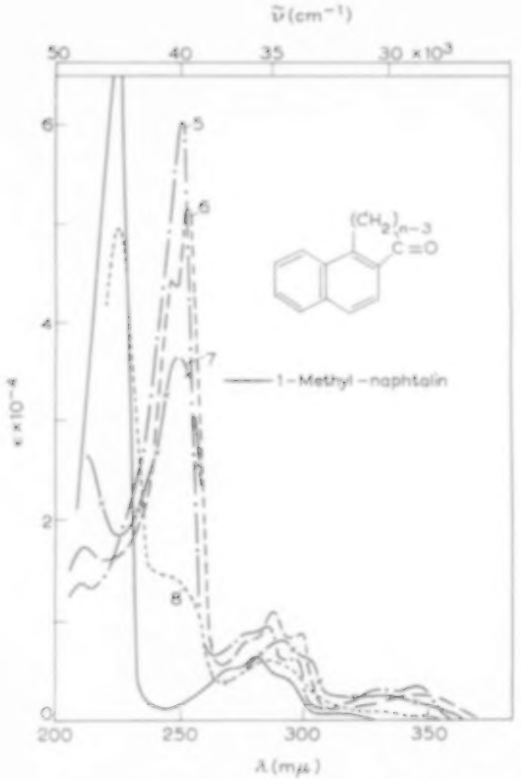


ABB. 1. UV-Absorption der Naphtho-[1',2':1,2]-cyclenone-(3) (IV) in Äthanol. Die Zahlen neben den Maxima geben die Ringgrösse *n* an.

Während die auf die spektrale Anregung des konjugierten Systems CO-Kern zurückgehende Bande bei 250 mμ beim Übergang zum mittleren Ringgebiet an Extinktion einbüsst, erhebt sich bei 225 mμ eine neue Bande, die im Spektrum von IV, $n = 5, 6$ fehlt und bei IV, $n = 8$ mit $\epsilon = 50\,000$ eine beachtliche Extinktion erreicht. An der gleichen Stelle findet sich eine scharfe Bande des 1-Methyl-naphthalins ($\lambda = 224$ mμ; $\epsilon = 75\,000$), dessen Spektrum in Abb. 1 zum Vergleich mitaufgenommen wurde. In den Ketonen IV beobachten wir somit mit steigender Ringgrösse eine *Änderung des spektralen Typus:* Das aromatische Keton geht mit zunehmender Entkoppelung zwischen Carbonyl und Kern in den Typus des 1-Alkyl-naphthalins über.

[16] Übersicht: R. Huisgen *Angew. Chem.* **69**, 341 (1957).

Noch hübscher lässt sich dieses Phänomen in den UV-Spektren der 2,4-Dinitrophenyl-hydrazone der Ringketone IV erkennen (Abb. 2). Infolge der *geringeren Koppelungsenergie* zwischen CN-Doppelbindung und aromatischem Kern hat die Mittlere-Ring-Torsion in Oximen und Hydrazonen eine stärkere Mesomeriehinderung als in den aromatischen Ketonen zur Folge. Die typische Absorptionsbande des konjugierten 2,4-Dinitrophenyl-hydrazons von IV, $n = 5$, 6 bei 387–390 mμerleidet mit steigender Ringgrösse eine Verschiebung gegen kürzere Wellen bei gleichz eitiger Extinktionsabnahme. Die geometrisch-isomeren Dinitrophenyl-hydrazone von IV,

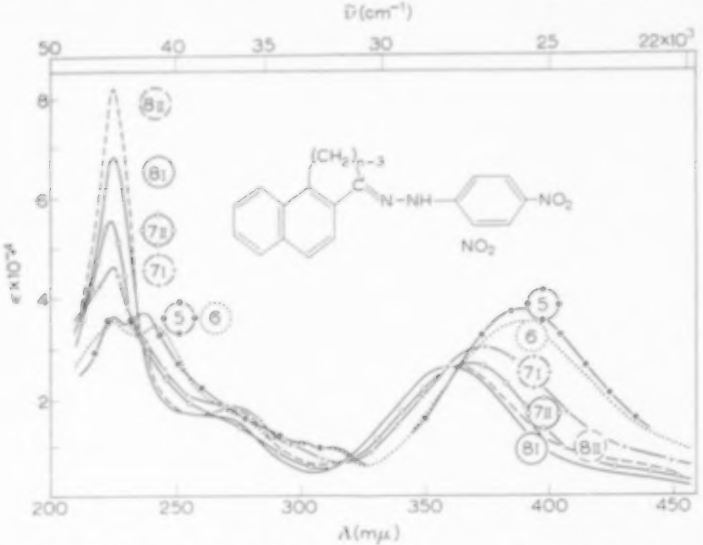


Abb. 2. UV-Absorption der 2,4-Dinitrophenyl-hydrazone der Naphto-cyclenone IV in Dioxan. Die Zahlen entsprechen den Ringgrössen *n*.

$n = 8$ zeigen das Maximum bei 362 mμ; bei 363 mμ wurde das des Aceton-2,4-dinitrophenyl-hydrazons, also des arylfreien Grundkörpers, gefunden. Symbath mit der Entkoppelung zwischen Naphthalin- und Hydrazonsystem geht das Aufsteigen einer neuen Bande bei 225 mμ, die in den isomeren Hydrazonen von IV, $n = 8$ eine Extinktion von 68 000 bezw. 82 000 erreicht; diese Bande ist wiederum der spektralen Anregung des 1-Alkyl-naphthalin-Systems zuzuordnen. *Mit dem Übergang zum mittleren Ringgebiet geht somit das Absorptionsspektrum des konjugierten Systems in das Summenspektrum der entkoppelten Teilsysteme über.*

Auch die Farben der *kristallisierten* 2,4-Dinitrophenyl-hydrazone verraten bereits den bis zur Löschung fortschreitenden Konjugationsrückgang. Die weinrote Farbe des Derivats von IV, $n = 6$ findet sich im 7-gliedrigen Ring bereits auf orange aufgehellt; die isomeren Hydrazone des 8-gliedrigen Ketons weisen die gleiche gelbe Farbe auf wie das Derivat des Acetons.

Offensichtlich vermindert die sterische Mesomeriehinderung auch die Gitterenergie der kristallisierten Ketone IV und ihrer Carbonylabkömmlinge. Ob für das aus Tabelle 2 ersichtliche *Sinken der Schmelzpunkte* beim Übergang vom 5- zum 8-gliedrigen Ring lediglich räumliche oder auch elektronische Faktoren massgebend sind, bleibe dahingestellt.

TABELLE 2. SCHMELZPUNKTE DER NAPHTHO-CYCLENONE IV UND IHRER DERIVATE

	Ringgrösse *n*			
	5	6	7	8
Keton	121°	96°	63°	82°
Semicarbazon	270°	245°	242°	195°
Oxim	227°	171°	180°	183°
2,4-Dinitrophenyl-hydrazon	291°	278°	231°	209°

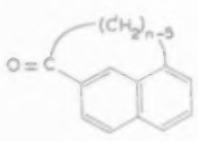
(c) *Die intramolekulare Acylierung der höheren ω-(1-Naphthyl)-fettsäuren*

Bei der Cyclisierung der höheren Aryl-fettsäure-chloride bietet das Naphthalinsystem naturgemäss eine grössere Zahl von Ausweichmöglichkeiten als dem Benzolderivat zur Verfügung stehen. Die Vermutung, dass sich bereits die Säuren III, $m = 7, 8$ der Schliessung der konformativ so ungünstigen 9- und 10-gliedrigen Ringe gegen die Position 2 (IV, $n = 9, 10$) entziehen, bestätigte sich.

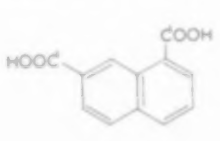
Viele der rohen Cyclisierungsprodukte zeigten nach der Hochvakuumdestillation nur geringe Kristallisationsneigung. Eine Reinigung bezw. Trennung von Isomerengemischen wurde bei der Adsorption aus Petroläther an Aluminiumoxyd erzielt, wobei die UV-Fluoreszenz die Indikation der Fraktionen ermöglichte. Wo die Kristallisation des Ketons nicht gelang, konnten meist kristalline Oxime, Semicarbazone oder 2,4-Dinitrophenyl-hydrazone erhalten werden.

Die Oxydation der Ringketone mit Permanganat oder Salpetersäure zu Benzolpolycarbonsäuren vermochte nur zu entscheiden, ob es sich um Produkte einer *homo-oder heteronuclearen* Acylierung handelte. Wies die Isolierung der Benzol-1,2,3-tricarbonsäure auf den letzten Reaktionstyp, so liess die Oxydation zu Benzol-1,2,3,4-tetracarbonsäure die Möglichkeiten eines Ringschlusses gegen die Positionen 2 und 4 offen. Als wertvolles Hilfsmittel erwies sich dagegen die schon von Weissgerber und Kruber[17] verwendete Oxydation mit alkalischem Kalium-ferricyanid, die sich auf die aliphatische Seitenkette beschränkt und den Naphthalinkern unangetastet lässt. Die Nachteile der nötigen langen Reaktionszeit und der bescheidenen Ausbeute wurden durch die gute Charakterisierung der Naphtalindicarbonsäuren über ihre kristallisierten Dimethylester etwas wettgemacht.

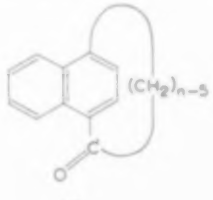
Überraschenderweise ergab sich die *Position 7 als bevorzugter Acylierungsort* für die 1-Naphthyl-fettsäuren III, $m = 7$–10. Die Oxydation zur 1,7-Dicarbonsäure (VIII) ist nur mit der Konstitution VII der Ringketone vereinbar. Daneben liess sich bei III, $m = 10$ auch die 1,4-Angliederung des Ketonringes zu IX, parallel zu den



VII



VIII



IX

[17] R. Weissgerber und O. Kruber *Ber. Dtsch. Chem. Ges.* **52**, 346 (1919); s. a. L. Ruzicka und E. A. Rudolph *Helv. Chim. Acta* **10**, 915 (1927); M. F. Ansell *J. Chem. Soc.* 575 (1954).

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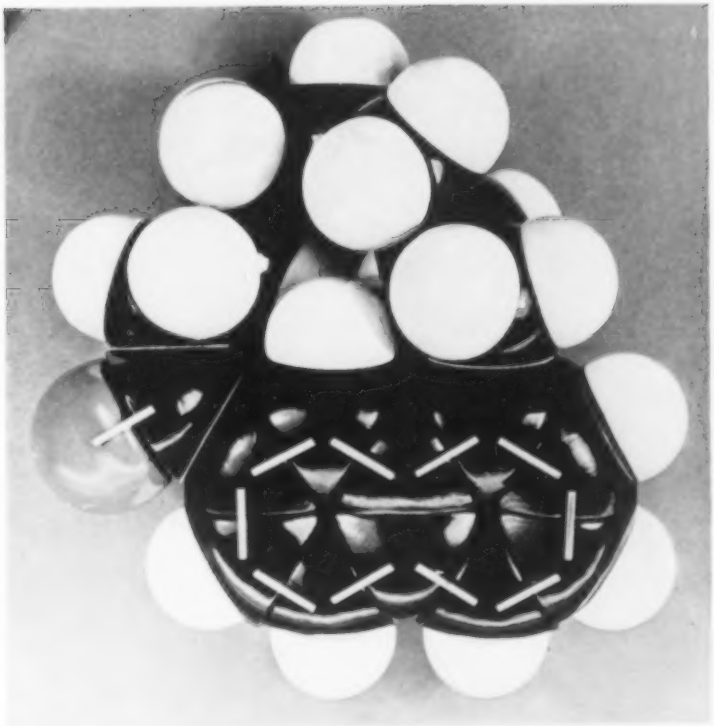

Abb. 3. Molekülmodell des Ketons 1,7-(β12) (VII, $n = 12$) aus Stuart-Briegleb Kalotten.

Verhältnissen in der ω-Phenyl-fettsäure-Reihe,[2] mittels Überführung in Naphthalin-1,4-dicarbonsäure nachweisen. Die Tabelle 3 fasst die Resultate zusammen.

Eine kurze Bemerkung zur Nomenklatur: Das Keton VII, $n = 12$ lässt sich korrekt, aber schwerfällig, als Naphtho-[1′,9′,8′,7′:1,2,3,4]-*cyclo*decen-(3)-on-(5) oder kürzer als 8′-Oxo-1,7-octamethylen-naphthalin kennzeichnen. Kürzer und nicht minder eindeutig in der folgenden Diskussion ist die Bezeichnung als Keton 1,7 (β 12), wobei die vorausgestellten Zahlen den Annellierungstyp und die Zeichen in der Klammer die Stellung der Carbonylgruppe am Naphthalinkern sowie die Gliederzahl des Ketonringes angeben.

TABELLE 3. INTRAMOLEKULARE ACYLIERUNG DER ω-(1-NAPHTHYL)-FETTSÄUREN III, $m = 7$–10

Säurechlorid vom III, m=	Eintropfgeschwindigkeit in mMol/Stde.	Rohausb. in % d.Th.	Konstitution der Ringketone
7	0,56	3,5	VII, $n = 11$ (?)
8	0,76	9,6	VII, $n = 12$; Schmp. 134°
9	0,64	9,3	VII, $n = 13$ (?) + IX, $n = 13$ (?)
10	0,62	33	VII, $n = 14$; Schmp. 107° + IX, $n = 14$

Schon das Kalottenmodell lässt entgegen der Erwartung für die 1,7(β)-Ketone VII *keine sterische Mesomeriehinderung* im mittleren Ringgebiet voraussehen. Der kleinste Ketonring VII, der sich leidlich ohne Baeyer-Spannung am Modell schliessen lässt, ist der mit $n = 11$. Die Carbonylgruppe wird dabei nicht gezwungen, die Kernebene zu verlassen, wie es Abb. 3 für das nächsthöhere Homologe zeigt.

In schöner Übereinstimmung mit der Modellbetrachtung sprechen die UV-Spektren der Ketone VII, $n = 12$, 14 in Abb. 4 für eine *uneingeschränkte Koppelung* zwischen Carbonyl und Naphthalinkern. Die Bande des konjugierten Systems erreicht die gleiche Extinktion wie etwa in IV, $n = 6$ (Abb. 1). Auch die UV-Absorption des Oxims von VII, $n = 12$ zeigt die Koplanarität des π-Bindungssystems an. Die rote Farbe der 2,4-Dinitrophenyl-hydrazone von VII, $n = 12$, 14 ist die des Derivats von IV, $n = 6$.

Da die intramolekulare Acylierung unter den von uns gewählten Reaktionsbedingungen nicht voll reversibel ist, geht es nicht an, die bevorzugte Acylierung in 7 mit der ungehinderten Konjugation des Ketons VII zu begründen. In der üblichen σ-Bindungs-Zwischenstufe der Kernsubstitution ist die Position 7 ein tetraedrisches Zentrum, das der Carbonylgruppe keinerlei Konjugation zu vermitteln vermag. Das konjugierte System wird erst in der nicht länger geschwindigkeitsbestimmenden Folgereaktion ausgebildet. Die Begründung liegt vielmehr in der *Stabilisierung der kationischen Zwischenstufe*. Von dem Hyperkonjugationseffekt der Methylengruppe der Fettsäure-Seitenkette in 1 profitiert die Substitution in den Positionen 2,4 > 5,7. Der Ringschluss in 2 kann bei den Säuren III, $n = 7$–10 nur mit einem Übermass ungünstiger Konformationen in der Polymethylenkette erkauft werden. Die Substitution in 4 zu IX wird von der Baeyer-Spannung erst von IX, $n = 13$ an erlaubt. Da die Acylierung in Stellung 5 eine wesentlich grössere Spannweite des Ketonrings erfordert, bleibt die Position 7 als günstigste für die Ringangliederung übrig.

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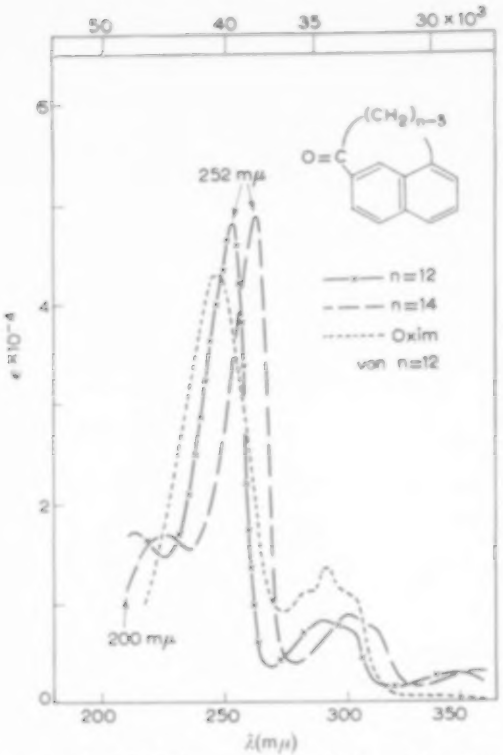

ABB. 4. UV-Absorption der 1,7-(β)-Ketone VII, $n = 12, 14$ und des Oxims von VII, $n = 12$ in Äthanol. (Die Kurve für VII, $n = 14$ wurde der Übersichtlichkeit halber um 10 mμ nach rechts verschoben.)

BESCHREIBUNG DER VERSUCHE

Darstellung der ω-(1-Naphthyl)-fettsäuren

β-(1-Naphthyl)-propionsäure (III, $m = 3$)

Die mit 1-Chlormethyl-naphthalin[18] durchgeführte Malonestersynthese folgte den Literaturangaben.[7] Das Säurechlorid wurde nach dem Abziehen des überschüssigen Thionylchlorids aus Ligroin umkristallisiert; Schmp. 65–66,5° (54°[12]).

γ-(1-Naphthyl)-buttersäure (III, $m = 4$)

Günstiger als die Umsetzung des Naphthalin smit Succinanhydrid erwies sich die Acylierung mit Bernsteinsäure-monoäthylester-chlorid.[19] Die Kristallisation der isomeren *β-(1-Naphthoyl)-propionsäuren* aus heissem Eisessig gab annähernd reine 2-Naphthyl-verbindung;[6] das aus der Mutterlauge mit Wasser abgeschiedene, bei 119–126° schmelzende 1-Isomere war noch nicht rein (Schmp. 131–132°[6]). Auch andere Trennungsmethoden gaben keine isomerenfreie 1-Naphthoyl-säure.[20] Eine Reinigungsmöglichkeit bot das Umlösen der bei der Clemmensen–Martin-Reduktion[9] erhaltenen γ-(1-Naphthyl)-buttersäure.

[18] O. Grummit und A. C. Buck *J. Amer. Chem. Soc.* **65**, 295 (1943).
[19] D. Papa, E. Schwenk und H. Hankin *J. Amer. Chem. Soc.* **69**, 3018 (1947).
[20] N. L. Drake und W. C. McVey *J. Org. Chem.* **4**, 464 (1939); M. S. Newman, R. B. Taylor, T. Hodgson und A. B. Garrett *J. Amer. Chem. Soc.* **69**, 1784 (1947).

δ-(1-Naphthyl)-valeriansäure (III, $m = 5$)

3-(1-*Naphthyl*)-n-*propanol*. 0,48 Mol. des bei 140–142°/0,5 Torr übergehenden und bei 35,2–36° schmelzenden *β-(1-Naphthyl)-propionsäure-methylesters* wurden in 300 cm³ abs. Äther gelöst und in 0,25 Mol. Lithium-aluminiumhydrid in 270 cm³ Äther innerhalb 40 Min. eingetropft und noch 2 Stdn. rückflussgekocht. Nach saurer Hydrolyse erhielten wir das Carbinol als farbloses Öl vom Sdp. 125–127°/0,01 Torr; Ausb. 96% d.Th.

3-(1-*Naphthyl*)-n-*propyl-bromid*. 86 g Carbinol wurden mit 140 cm³ 48%-Bromwasserstoffsäure und 2 g rotem Phosphor 6 Stdn. gekocht und nach Zusatz von 20 cm³ konz. Schwefelsäure weitere 6 Stdn. unter Rückfluss zum Sieden erhitzt. Nach Aufarbeitung mit Wasser-Äther ging das Bromid bei 127–130°/0,4 Torr in 94% Ausb. über.

Malonester-Synthese. In die Lösung von 0,40 g-Atomen Natrium in 320 cm³ abs. Äthanol wurden 0,66 Mol. Malonester und alsdann 0,174 Mol. Naphthyl-propylbromid unter Rühren bei Raumtemp. eingetragen. Nach 6-stdg. Rückflusskochen wurde mit angesäuertem Eiswasser und Äther aufgearbeitet; bei 183–189°/0,01 Torr destillierten 0,131 Mol. *γ-(1-Naphthyl)-propyl-malonsäure-diäthylester*. Die alkalische Verseifung und Decarboxylierung bei 175° vollzogen sich mit 90% Ausbeute. Die *δ-(1-Naphthyl)-valeriansäure* kam aus Petroläther in farblosen Nadeln vom Schmp. 88,6–89,1°.

$C_{15}H_{16}O_2$ (228,28) Ber. C 78,91 H 7,06
Gef. C 78,78 H 7,10

Die Säure III, $m = 5$ wurde bereits aus III, $m = 4$ durch *Arndt–Eistert-Kettenverlängerung* bereitet.[21] Bei der Nacharbeitung wurden 48% d.Th. an δ-(1-Naphthyl)-valeriansäure erhalten; für die Bereitung grösserer Mengen ist die oben beschriebene Methode weit vorteilhafter. Auch die über das Diazoketon dargestellte Säure schmolz bei 88,0–88,7° (78–80°[21]).

Gef. C 78,65 H 6,68

ε-(1-Naphthyl)-capronsäure (III, $m = 6$)

δ-(1-Naphthoyl)-valeriansäure. In eine gekühlte Grignard-Lösung aus 70,0 g reinem α-Brom-naphthalin (0,338 Mol.) und 8,1 g Magnesiumspänen in 250 cm³ Äther wurden unter energischer Rührung und Durchleiten von Stickstoff 34 g trockenes Cadmium-chlorid portionsweise innerhalb 10 Min. eingetragen. Nach 40 Min. Rückflusskochen wurde der grösste Teil des Solvens abdestilliert und nach Zusatz von 100 cm³ trockenem Benzol der Rest des Äthers übergetrieben. Alle Reaktionen, auch das erneute Suspendieren in 200 cm³ Benzol, wurden unter kräftigem Turbinieren ausgeführt, um ein Zusammenballen des unlöslichen Dinaphthyl-cadmiums zu verhindern. Unter Kühlung wurden 58,0 g Adipinsäure-äthylester-chlorid (0,302 Mol.) in 50 cm³ Benzol eingetropft; je 1 Stde. Rühren bei 40° und bei Siedetemperatur brachte die Reaktion zum Abschluss. Nach Aufarbeitung mit verd. Schwefelsäure und Äther ging der *δ-(1-Naphthoyl)-valeriansäure-äthylester* bei 190–200°/0,4 Torr über: 55,3 g (65% d.Th.). Die Verseifung in methanolischer Kalilauge gab die freie Säure (99% d.Th.) als langsam kristallisierendes Öl.

Wolff–Kishner-*Reduktion*. 49,5 g Ketosäure erhitzten wir mit 50 g Ätzkali und 37 cm³ 80%-Hydrazinhydrat in 250 cm³ Diäthylenglykol 8 Stdn. im 130–135°-Ölbad.

[21] W. Bachmann und R. O. Edgerton *J. Amer. Chem. Soc.* **62**, 2219 (1940).

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Nach Abziehen des Wassers und überschüssigen Hydrazinhydrats wurde langsam die Temperatur gesteigert, wobei die Stickstoff-Freisetzung gegen 175° flott wurde. Nach 3 Stdn. bei 200–210° liessen wir auf 90° abkühlen und gossen auf verd. Salzsäure + Eis. Die Rohsäure wurde noch einmal in wässrigem Alkali gelöst, mit Äther von Neutralstoffen befreit sowie nach Reinigung mit Entfärbungskohle angesäuert und in Äther aufgenommen. Nach Abdampfen des Lösungsmittels wurde die langsam kristallisierende Säure mehrfach mit viel Petroläther (40–80°) ausgekocht, wobei Verunreinigungen zurückblieben. Beim Erkalten und nach Einengen der Lösung kristallisierten 39,0 g *ε*-(1-*Naphthyl*)-*capronsäure* (83% d.Th) vom Schmp. 77–79° aus. Nach mehrfachem Umlösen farblose Spiesse vom Schmp. 78,6–79.2°.

$C_{16}H_{18}O_2$ (242,30) Ber. C 79,30 H 7,49
Gef. C 79,19 H 7,09

Die Clemmensen-*Reduktion* der Ketosäure mit Toluolzusatz lieferte nach 50 Stdn. Kochen nur 54% d. Th. einer bei 72–78° schmelzenden Säure.

Die Acylierung des Naphthalins mit Adipinhalbester-chlorid und Aluminiumchlorid in Nitrobenzol fand sich bereits beschrieben;[22] bei der mühsamen Isomerentrennung des zu 64% anfallenden Gemischs erhielten Fieser und Smuszkovicz[22] nur 3,6% reiner 1-Naphthoyl-Verbindung über das Semicarbazon. Bei der *Friedel–Crafts Reaktion* in Tetrachlor-äthan gelangten wir zu 18% d.Th. an roher *δ*-(1-*Naphthoyl*)-*valeriansäure* und 44% des 2-Isomeren.

ζ-(1-*Naphthyl*)-*önanthsäure* (III, $m = 7$)

7-(1-*Naphthyl*)-4-*oxo-heptylsäure* 54,8 g 3-(1-Naphthyl)-propyl-bromid traten mit Jod-angeätztem Magnesium in Reaktion und wurden nach Überführung in die Cadmium-Verbindung, wie oben beschrieben, mit 36,2 g Bernsteinsäure-äthylesterchlorid umgesetzt. Der Ketoester wurde ohne Destillation verseift und die freie Ketosäure durch Umfällen aus Natronlauge gereinigt: 37,1 g (62% d.Th.) vom Schmp. 113–119°.

Die Wolff–Kishner-*Reduktion* wurde wie S. 279 durchgeführt. Die Reinigung erfolgte vorteilhaft über den bei 154–159°/0,1 Torr übergehenden Methylester. Die mit 72% d.Th. anfallende freie *Naphthyl-önanthsäure* schmolz bei 62–63°; nach Umlösen aus Benzin farbl. Blättchen vom Schmp. 64,4–65,0°.

$C_{17}H_{20}O_2$ (256,33) Ber. C 79,65 H 7,86
Gef. C 79,46 H 8,07

η-(1-*Naphthyl*)-*caprylsäure* (III, $m = 8$)

Korksäure-monomethylester-chlorid. 1,73 Mol. Korksäure und 1,73 Mol. Methanol wurden mit 25 cm³ konz. HCl durch 8-stdg. Rückflusskochen verestert. Nach einem Diester-Vorlauf ging der Halbester bei 162–184°/11 Torr über und wurde mittels einer Passage über das Natriumsalz gereinigt; Schmp. 17–18°. Die als Rückstand verbleibende Korksäure wurde mit dem verseiften Diester erneut in den Prozess eingeführt. Das mit Thionylchlorid bereitete Monomethylester-chlorid destillierte bei 134–136°/11 Torr; es wurde erst unmittelbar vor der Verwendung dargestellt.

7-(1-*Naphthoyl*)-*heptylsäure*. 150 mMol. Di-(1-naphthyl)-cadmium wurden wie S. 279 mit 31,0 g Korksäure-esterchlorid (150 mMol.) zur Reaktion gebracht. Nach

[22] L. Fieser und J. Smuszkovicz *J. Amer. Chem. Soc.* **70**, 3352 (1948).

zweimaliger Destillation bei 175–178°/0,001 Torr fielen 33,5 g Ketoester (75% d.Th.) vom Schmp. 29–33° an. Die freie Säure schmolz nach Umlösen aus Benzin bei 69,5–71°.

Die Wolff–Kishner-*Reduktion* mit Reinigung über den Methylester vom Sdp. 156–159°/0,001 Torr folgte obigem Beispiel. Die *η-(1-Naphthyl)-caprylsäure* kam aus Petroläther in Nadeln vom Schmp. 58,0–58,8°. Ein aus dem Mikrokölbchen bei 170°/0,2 Torr übergetriebenes Präparat wurde analysiert.

$C_{18}H_{22}O_2$ (270,36) Ber. C 79,96 H 8,20
Gef. C 80,09 H 8,25

ω-(1-Naphthyl)-pelargonsäure (III, $m = 9$)

η-(1-Naphthoyl)-caprylsäure. 180 mMol. Di-naphthyl-cadmium wurden mit 44 g des bei 125–127°/1 Torr übergehenden Azelainsäure-monomethylester-chlorids umgesetzt. Der als farbloses Öl bei 183–187°/0,01 Torr destillierende Ketoester (47,8 g) wurde mit methanolischer Kalilauge verseift: 44,8 g Ketosäure vom Schmp. 74,5–76,5°.

Das in 75% d.Th. bei der Wolff–Kishner-*Reduktion* anfallende Rohprodukt schmolz bei 59,0–60,7°. Aus Petroläther (40–60°) kristallisierte die farblose *9-(1-Naphthyl)-nonylsäure* in glänzenden Blättchen vom Schmp. 61,0–61,7°. Erst eine bei 172°/0,2 Torr destillierte Probe gab richtige Analysenwerte.

$C_{19}H_{24}O_2$ (284,38) Ber. C 80,24 H 8,51
Gef. C 79,91 H 8,47

ω-(1-Naphthyl)-caprinsäure (III, $m = 10$)

Die Reinigung des Sebacinsäure-monomethylesters erfolgte, wie früher für den -monoäthylester beschrieben.[2] Das mit reinem Thionylchlorid bereitete Ester-chlorid muss unmittelbar im Anschluss an die Darstellung durch Hochvakuum-Destillation gereinigt werden. Die Reaktion mit Di-(1-naphthyl)-cadmium in Benzol gab den Ketoester vom Sdp. 200–205°/0,01 Torr; dessen Vereifung führte zur farblosen *ω-(1-Naphthoyl)-pelargonsäure* (73% d.Th.) vom Schmp. 66–68,5°.

Bei der Reduktion wurde in 84% Ausb. die Aryl-fettsäure erhalten, die nach Umlösen aus Ligroin Schmp. 71,8–72,4° aufwies.

$C_{20}H_{26}O_2$ (298,41) Ber. C 80,49 H 8,78
Gef. C 80,50 H 8,87

ω-(1-Naphthyl)-palmitinsäure (III, $m = 16$)

180 mMol. Di-(1-naphthyl)-cadmium wurden mit 200 mMol. *Thapsiasäure-monomethylester-chlorid* in Benzol zur Reaktion gebracht. Die nicht umgesetzten Anteile des Thapsia-halb- und -diesters wurden bis 220°/0,001 Torr entfernt. Bei der Verseifung des hellgelben Rückstandes fielen 130 mMol. (65% d.Th.) roher Ketosäure vom Schmp. 58–67° an. Aus Ligroin kam die reine *15-(1-Naphthoyl)-pentadecansäure* in sternchenförmig vereinigten Nadeln vom Schmp. 71,0–72,0°.

$C_{26}H_{36}O_3$ (396,55) Ber. C 78,74 H 9,15
Gef. C 79,01 H 9,27

Die Wolff–Kishner-*Reduktion* vollzog sich mit 84% Rohausb. und gab ein

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Präparat vom Schmp. 59–63,5°. Die reine *ω-(1-Naphthyl)-palmitinsäure* kristallisierte aus Petroläther (40–60°) in farblosen Drusen vom Schmp. 68,5–69,0°.

$C_{26}H_{38}O_2$ (382,56) Ber. C 81,62 H 10,01
Gef. C 81,61 H 9,75

Intramolekulare Acylierung in hoher Verdünnung

Da die Säurechloride der höheren Naphthyl-fettsäuren nicht mehr unzersetzt flüchtig sind, verzichteten wir auf die Destillation und verfuhren folgendermassen: 20–40 g reiner Carbonsäure wurden mit 1,5 Moläquival. Phosphorpentachlorid in 50–100 cm³ abs. Methylenchlorid 1 Stde. zum Sieden erhitzt. Das nach Entfernung des Solvens sowie des Phosphoroxychlorids und des überschüssigen Pentachlorids im Wasserstrahlvakuum zurückbleibende Säurechlorid war meist als Ergebnis von Nebenreaktionen dunkel gefärbt. Es wurde unmittelbar in trockenem Schwefelkohlenstoff aufgenommen und in die intramolekulare Acylierung eingeführt.

Die Apparatur und Ausführung der Hochverdünnungs-Cyclisierung entsprach den früheren Angaben.[2] 100–200 g Aluminium-chlorid, in der Kugelmühle gepulvert, wurden in Suspension in Schwefelkohlenstoff vorgelegt. Während des 100–150 Stdn. beanspruchenden Zutropfens des Säurechlorids wurden alle 30–40 Stdn. 50 g gepulv. Aluminiumchlorid durch einen mit Schliffstopfen versehenen Einfüllstutzen nachgefüllt. Schon wenige Stunden nach Beginn setzte eine Dunkelfärbung der Cyclisierungslösung ein, dem sich bald die Ausscheidung schwarzbrauner Krusten an Kolbenwand und Rührer anschloss.

Zur Aufarbeitung wurde der Schwefelkohlenstoff abdestilliert und der Rückstand mit 1,5 kg Eis und 0,5 kg konz. Salzsäure hydrolysiert; mit kräftigem Schütteln unter Zusatz von Benzol erzielte man eine Ablösung der Krusten. Nach Absaugen und Waschen mit Wasser wurden die Krusten getrocknet und aus der Hülse mit dem abgetrennten Benzol extrahiert. Beim anschliessenden Trocknen der Benzolphase mit Kalium-carbonat wurden saure Verunreinigungen entfernt. Nach Abziehen des Solvens gingen die rohen Naphtho-cyclenone bei der Hochvakuumdestillation aus dem Schmitt–Coutelle-Kolben[23] über. Die gelbe oder gar dunkelbraune Färbung der Destillate liess sich durch wiederholte Destillation oder durch Adsorption aus Petroläther an Aluminiumoxyd weitgehend beseitigen. Nach dimeren und trimeren Cyclisierungsprodukten[3,24] wurde nicht gefahndet. Tabelle 4 fasst die Ansätze zusammen.

TABELLE 4. CYCLISIERUNG DER ω-(1-NAPHTHYL)-FETTSÄURE-CHLORIDE IN HOHER VERDÜNNUNG

Säurechlorid von III, m = mMol		in Ltr. CS_2	zugetropft zu $AlCl_3$ in g	in Ltr. CS_2	innerhalb Stdn.	Rohketon in % d.Th.
5	65,8	0,7	100	2,4	26	96
6	80,4	2	220	4	81	70
7	61,3	2	100	4	109	3,5
8	96,6	2	200	4	127	10
9	96,5	2	220	4	150	9
10	77,8	2	300	4	125	33

[23] H. Schmitt und E. Coutelle *Chem. Fabr.* **14**, 200 (1941).
[24] W. M. Schubert, W. A. Sweeney und H. K. Latourette *J. Amer. Chem. Soc.* **76**, 5462 (1954).

Die 1,2-(*β*)-*Naphtho-cyclen*-(1)-*one*-(3) (IV) *und Derivate*

4,5-*Benzo-indanon*-(1) (IV, $n = 5$)

Das nach[13] bereitete Ringketon kristallisierte nach wiederholter Hochvakuumsublimation in Nadeln vom Lit. Schmp. 120–121°.

Oxim. Wenn nicht anders beschrieben, wurde die Oximierung durch Kochen mit Hydroxylammonium-chlorid und Natriumhydrogencarbonat in Alkohol vorgenommen. Aus Äthanol Spiesse vom Schmp. 226,5–228°. Die Konjugation zwischen Oximdoppelbindung und aromatischem Kern zeigt sich in der Lichtabsorption: λ(Max.) = 253 mμ, ϵ = 42 000.

Semicarbazon. Aus Alkohol kristallisierte das Derivat in Prismen vom Zers. punkt 270° nach Verfärbung gegen 250°.

2,4-*Dinitrophenyl-hydrazon.* Die Reaktion vollzog sich mit dem alkoholisch-schwefelsauren Reagens[25] beim Stehen in der Kälte. Nach mehrfachem Umlösen aus heissem Nitrobenzol schmolzen die schwerlöslichen leuchtendroten Nadeln bei 291° u.Z.

$C_{19}H_{14}O_4N_4$ (362,33) Ber. C 62,98 H 3,90
Gef. C 63,33 H 3,89

1,2-*Naphtho*-cyclo*hexenon*-(3) (IV, $n = 6$)

Die Cyclisierung der γ-(1-Naphthyl)-buttersäure erfolgte mit heisser starker Schwefelsäure.[6] Aus Ligroin kam das Keton in Blättchen vom Schmp. 95,5–96,0° (95–96°[6]).

Oxim. Aus Methanol in regulären Prismen vom Schmp. 170,4–170,7° (165–166°[26]).

Semicarbazon. Beim 5-stdg. Kochen mit Semicarbazid-chlorhydrat und Natriumacetat in Alkohol wurden nach Umlösen aus dem gleichen Solvens Polyeder vom Schmp. 244–246° (247–250°[26]) erhalten.

2,4-*Dinitrophenyl-hydrazon.* Weinrote Stäbchen, die sich nach Umlösen aus viel Benzol oberhalb 278° zersetzten.

$C_{20}H_{16}O_4N_4$ (376,36) Ber. C 64,52 H 4,27
Gef. C 63,82 H 4,29

Oxydation. Die Salpetersäureoxydation wurde unter den für 1,4-Dimethylnaphtalin beschriebenen Bedingungen[27] ausgeführt. 150 mg Keton wurden mit 4 cm³ 40%-Salpetersäure 12 Stdn. im Einschlussrohr auf 175° ehritzt. Der farblose Eindampfrückstand schmolz nach mehrfachem Umlösen aus konz. Salpetersäure bei 232–236° (Mellophansäure 236°[27]) unter Anhydrisierung (37 mg). 15 mg der *Benzol*-1,2,3,4-*tetracarbonsäure* wurden in 2 cm³ Methanol mit ätherischer Diazomethan-Lösung verestert; der Tetramethylester kristallisierte aus *Cyclo*hexan: 12 mg vom Schmp. 125–126,5° (133–135°,[27] 129°[28]).

1,2-*Naphtho*-cyclo*heptenon*-(3) (IV, $n = 7$)

Aus 15 g III, $m = 5$ wurden nach der Verdünnungs-Cyclisierung des Säurechlorids

[25] R. L. Shriner, R. C. Fuson und D. Y. Curtin *The Systematic Identification of Organic Compounds* (4. Aufl.) S.219. Wiley, New York (1956).
[26] G. Schröter, H. Müller und J. Y. Huang *Ber. Dtsch. Chem. Ges.* **62**, 656 (1929).
[27] H. Bamford und J. L. Simonsen *J. Chem. Soc.* **97**, 1904 (1910).
[28] K. Warnat *Ber. Dtsch. Chem. Ges.* **58**, 2768 (1925).

13,3 g des bei 120–123°/0,01 Torr übergehenden und bei 59–62° schmelzenden Rohketons erhalten. Aus Petroläther (40–60°) kam das Ringketon in derben Spiessen vom Schmp. 62,3–62,7°.

$C_{15}H_{14}O$ (210,26) Ber. C 85,68 H 6,71
Gef. C 85,64 H 6,57

Oxim. Aus 1,0 g Keton wurden 0,89 g Oxim erhalten. Aus Alkohol in Nadeln vom Schmp. 179,7–180,3°. Mit einem UV-Absorptionsmaximum bei 240 mμ ist die Bande des $N \rightarrow V_1$-Übergangs bereits kräftig hypsochrom verschoben als Folge der Mittleren-Ring-Torsion.

$C_{15}H_{15}ON$ (225,28) Ber. C 79,97 H 6,71
Gef. C 80,26 H 6,78

Semicarbazon. Aus Alkohol kristallisierten glänzende Blättchen vom Schmp. 241,0–242,5°.

2,4-*Dinitrophenyl-hydrazone.* Aus Toluol feine, orangefarbene Nadeln vom Schmp. 230,5–231,5°.

$C_{21}H_{18}O_4N_4$ (390,39) Ber. C 64,60 H 4,65
Gef. C 64,64 H 4,39

Zu etwa 10% fand sich in der Mutterlauge ein leichter lösliches Isomeres, das aus Alkohol in gelborangefarbenen Nadeln vom Schmp. 165,3–166,5° kam.

Gef. C 65,35 H 4,75

Konstitutionsermittlung: Die Oxydation mit Salpetersäure (S. 283) gab *Mellophansäure*, die über ihren bei 128–129° schmelzenden Tetramethylester durch Mischschmp. identifiziert wurde.

1,2-*Naphtho*-cyclo*octenon*-(3) (IV, $n = 8$)

Das im Hochvakuum destillierte Rohprodukt wurde in benzolischer Lösung mit Natronlauge und Wasser gewaschen. Aus dem Claisenkolben ging das Keton bei 159–165°/0,3 Torr über. Aus Petroläther schied sich die reine Verbindung in rhombischen Prismen vom Schmp. 81,5–82° ab.

$C_{16}H_{16}O$ (224,29) Ber. C 85,67 H 7,19
Gef. C 85,45 H 7,01

Oxim. Die Reaktion in der Siedehitze führte zu einem Kristallisat von breitem Schmelzbereich, vermutlich einem Gemisch der geometrischen Isomeren. Der Umsatz durch Schütteln in der Kälte ergab ein leicht lösliches Oxim; Tieftemperaturkristallisation aus wenig Methanol lieferte Nadeln vom Schmp. 182,5–183,7°

$C_{16}H_{17}ON$ (239,30) Ber. C 80,30 H 7,16
Gef. C 80,18 H 7,08

Das UV-Spektrum zeigt die Bande des konjugierten Oxims nicht mehr. Das steile Maximum bei 227 mμ mit $\varepsilon = 73\,000$ entspricht ganz dem des 1-Methylnaphthalins.

Semicarbazon. Aus 60%-Alkohol Nadeln vom Schmp. 193,5–195°.

2,4-*Dinitrophenyl-hydrazone.* Beim Umsatz mit dem alkoholischen Reagens in der Wärme schied sich das schwerer lösliche Hydrazon als roter Kristallklumpen aus; nach dem Dekantieren kristallisierte beim Erkalten das leichter lösliche und hellergefärbte Isomere aus. Das erstgenannte kam aus viel Alkohol in orangefarbenen Polyedern vom Schmp. 195–196°.

$C_{22}H_{20}O_4N_4$ (404,41) Ber. C 65,33 H 4,99
Gef. C 65,52 H 4,93

Die langen Spiesse des gelben Isomeren schmolzen nach Umlösen aus wenig Alkohol bei 208,5–209°.

Gef. C 65,11 H 4,73

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Der bei 169–190° liegende Mischschmp. zeigt, dass es sich um Isomerie, nicht aber um Polymorphie handelt.

Oxydation. Aus 185 mg Keton wurden mit 40%-Salpetersäure (wie oben) 34 mg *Benzol*-1,2,3,4-*tetracarbonsäure* erhalten; Methylester-Schmp. 126–127,5°.

Cyclisierung der ζ-(1-*Naphthyl*)-*önanthsäure* (III, $m = 7$)

Die intramolekulare Acylierung des Säurechlorids aus 15,7 g Säure gab nur 0,51 g eines gegen 140°/0,01 Torr übergehenden, noch gefärbten Öls. Nach erfolglosen Kristallisationsversuchen wurde das 2,4-Dinitrophenyl-hydrazon in der Wärme bereitet. Das als dunkelrotes Harz anfallende Material wurde in Benzol an einer Aluminiumoxydsäule aufgezogen und mit Benzol entwickelt. Aus der unteren orangeroten Schicht konnte nach dem Durchlaufen ein orangefarbenes 2,4-*Dinitrophenyl-hydrazon* isoliert werden, das nach Umlösen aus Methanol bei 232–234° u.Z. schmolz. Die Ausbeute entsprach 30% d.Th, bezogen auf das Rohketon.

$C_{23}H_{22}O_4N_4$ (418,44) Ber. C 66,01 H 5,30
Gef. C 66,12 H 5,24

Es handelt sich vermutlich um das Derivat von VII, $n = 11$. UV-Maxima: λ_1 und $\lambda_2 = 230$ und 375 mμ; ϵ_1 und $\epsilon_2 \times 10^3 = 42{,}3$ und 27,6.

Cyclisierung der η-(1-*Naphthyl*)-*caprylsäure* (III, $m = 8$)

8′-*Oxo*-1,7-*octamethylen-naphthalin* (VII, $n = 12$)

Zwei gleichartig durchgeführte Ansätze lieferten 9,6 bezw. 7,7% d.Th. an destilliertem Rohketon. Nach Entsäuern mit verd. Natronlauge—vor der Hochvakuumdestillation führte diese Operation zur Bildung hartnäckiger Emulsionen—ging das Keton bei 140–150°/0,001 Torr aus dem Mikrokölbchen über. Beim Stehen in wenig Petroläther kristallisierte ¼ bis ⅓ des Materials in farblosen Polyedern.

Es sei hier schon betont, dass der ölige Anteil der Mutterlauge überwiegend aus dem gleichen Keton besteht. Aus dem Öl wurde nämlich das gleiche Semicarbazon erhalten wie aus dem kristallisierten Keton. Auch die chromatographische Reinigung des Öls mit anschliessender Ferricyanid-Oxydation gestattete uns den Nachweis der 1,7-Annellierung. Im folgenden werden nur die Reaktionen des kristallisierten Ketons beschrieben.

Nach mehrfachem Umlösen aus wenig Petroläther (40–60°) schmolz das *Keton* bei 133,6–134°.

$C_{18}H_{20}O$ (252,34) Ber. C 85,67 H 7,99
Gef. C 85,45 H 8,09

Oxim. Nach Umlösen aus Methanol zeigten die Nadeln Schmp. 216,5–217,5°.

$C_{18}H_{21}ON$ (267,36) Ber. C 80,86 H 7,92
Gef. C 80,71 H 7,93

Semicarbazon. Das aus Methanol umkristallisierte Derivat schmolz bei 215–217°, wurde oberhalb 220° wieder fest und zeigte bei 264–267° einen zweiten Schmp.

$C_{19}H_{23}ON_3$ (309,40) Ber. C 73,75 H 7,49
Gef. C 73,54 H 7,41

2,4-Dinitrophenyl-hydrazon. Das schon in der Kälte sofort abgeschiedene Derivat kristallisierte aus Benzol in zinnoberroten, glänzenden Blättchen vom Schmp. 259–260° u.Z.

$C_{24}H_{21}O_4N_4$ (432,46) Ber. C 66,65 H 5,59
Gef. C 66,64 H 5,61

Das UV-Spektrum ist das des vollkonjugierten Hydrazons: λ_1 und $\lambda_2 = 245$ und 387,5 mμ mit $\epsilon_1 = 33\,600$ und $\epsilon_2 = 35\,300$.

Oxydation. 212 mg feinpulv. Keton wurden mit einer Lösung von 120 g Kaliumferricyanid und 30 g Kaliumhydroxyd in 400 cm³ Wasser 120 Stdn. bei 70° turbiniert. Nach dem Erkalten und Filtrieren wurde mit Schwefelsäure angesäuert und 10 Stdn. mit Äther perforiert. Der Rückstand nach Abziehen des Aethers sublimierte bei 200–220°/0,2 Torr aus dem Mikrokölbchen: 38 mg vom Schmp. 255–270°. Der mit ätherischer Diazomethan-Lösung bereitete Dimethylester schmolz nach zweimaligem Umlösen aus Ligroin bei 83,4–86°. Der Mischschmp. mit einem authent. Präparat des *Naphthalin-1,7-dicarbonsäure-dimethylesters* lag bei 85–87°. Der ebenfalls bei 85–85,8° schmelzende 1,2-Naphthalsäure-dimethylester zeigte dagegen in der Mischung Schmp. 62–69°, also eine kräftige Depression.

Zur *Darstellung des Vergleichspräparats* wurde 7-Methyltetralon-(1) mit β-Phenyl-äthyl-magnesiumbromid umgesetzt; nach Dehydratisierung des tert. Carbinols mit wenig Salzsäure ging das 1-(β-Phenyl-äthyl)-7-methyl-3,4-dihydro-naphthalin bei 126–133°/0,01 Torr als zähes, leicht gefärbtes Öl in 71% Ausb. über. Beim Kochen mit 2,5 Mol.-Äquival. Chloranil in Xylol trat neben der Aromatisierung die Dehydrierung der β-Phenyläthyl-Seitenkette ein. Das *1-(ω-Styryl)-7-methyl-naphthalin*, das in Eisessig Brom entfärbte, wurde als Pikrat charakterisiert: Aus Methanol gelbe Nadeln vom Schmp. 106,4–107,3°.

$C_{25}H_{19}O_7N_3$ (473,42) Ber. C 63,42 H 4,05
Gef. C 63,63 H 4,60

Die geringe Wasserlöslichkeit des Kohlenwasserstoffs hat eine nur sehr langsame Oxydation zur Folge. Nach 120-stdg. Behandlung von 1,40 g Kohlenwasserstoff mit alkalischer Kaliumferricyanid-Lösung wie oben wurden nur 35 mg *1,7-Naphthalindicarbonsäure* erhalten. Der Dimethylester schmolz bei 85,8–87,2° (86–87°[29]).

[29] L. Ruzicka und J. A. van Melsen *Helv. Chim. Acta* **14**, 397 (1931).

Cyclisierung der ω-(1-Naphthyl)-pelargonsäure (III, $m = 9$)

Nach Entsäuern ging das Rohketon bei 140°/0,01 Torr aus dem Mikrokölbchen als gelbbraun gefärbtes Öl über. Die Entfärbung gelang durch Passieren einer kurzen Aluminiumoxydsäule in Petroläther-Lösung; keine Kristallisationsneigung.

$C_{19}H_{22}O$ (266,37) Ber. C 85,67 H 8,33
Gef. C 85,75 H 8,63

Die UV-Absorption ist der von VII, $n = 12$ ähnlich, jedoch ist die Extinktion geringer. Die Ursache liegt wohl im Vorhandensein eines Gemischs. Einen Hinweis auf die hier bereits einsetzende 4-Acylierung gab die Oxydation mit 40%-Salpetersäure bei 175° im Rohr (S. 283). Die bei 216–220° schmelzende Spitzenfraktion gabk eine Depression mit authent. Benzol-1,2,3,4-tetracarbonsäure.

Cyclisierung der ω-(1-Naphthyl)-caprinsäure (III, $m = 11$)

10'-Oxo-1,7-decamethylen-naphthalin (VII, $n = 14$) und *10'-Oxo-1,4-decamethylen-naphthalin* (IX, $n = 14$)

Das Rohketon (7,26 g) wurde entsäuert und destillierte bei 160–165°/0,04 Torr aus dem Claisenkolben (6,69 g). Auch nach Reinigung an Aluminiumoxyd kristallisierte das blassgelbe Öl nicht.

$C_{20}H_{24}O$ (280,39) Ber. C 85,67 H 8,63
Gef. H 85,69 H 8,32

Während die Salpetersäure-Oxydation wieder die *Benzol-1,2,3,4-tetracarbonsäure* mit Schmp. 225–229° als schwerlösliches Produkt zu isolieren gestattete, liess die Ferricyanid-Oxydation keinen Zweifel daran, dass ein Gemisch isomerer Ketone vorliegt. 750 mg wurden mit 50 g Kaliumferricyanid und 10 g KOH in 300 cm³ Wasser bei 60–70° 24 Stdn. gerührt und nach erneutem Zusatz von 50 g Oxydationsmittel weitere 24 Stdn. behandelt. Die Aufarb. wie oben gab 121 mg Sublimat. Mehrfaches Umlösen aus Eisessig führte zu einer 35 mg starken Spitzenfraktion vom Schmp. 300–310°. Der daraus mit Diazomethan bereitete Dimethylester schmolz nach Umkristallisieren aus Ligroin bei 65,0–66,5° und wies in der Mischung mit einem, gleichen Schmp. zeigenden, authent. Präparat von *Naphthalin-1,4-dicarbonsäure-dimethylester*[30] keine Depression auf. Dagegen wurde der Mischschmp. mit 1,7-Naphthalsäure-dimethylester bei 50–70° gefunden.

Aus der essigsauren Mutterlauge der Naphthalin-1,4-dicarbonsäure kristallisierten nach dem Einengen 34 mg vom Schmp. 290–298°. Der bei 85–87° schmelzende Dimethylester gab mit *Naphthalin-1,7-dicarbonsäure-dimethylester* keine Depression.

Die Trennung der isomeren Ketone gelang durch Chromatographie von 2 g an einer Aluminiumoxydsäule 80 × 2,5 cm aus Petroläther (40–80°). Die Entwicklung während mehrerer Tage wurde mittels UV-Fluoreszenz verfolgt; die Schichtentrennung war nicht ganz vollständig. Aus dem Durchlauf wurden folgende Anteile durch Hochvakuumdestillation isoliert:

	Fluoreszenz	mg	Gef. % C	% H
a	dunkelblau	88	86,71	9,22
b	blau	58	84,69	8,98
c	graublau	1370	85,78	8,72
d	hellblau	340		

[30] G. Lock und R. Schneider *Ber. Dtsch. Chem. Ges.* **84**, 636 (1951).

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Die kleinen Fraktionen *a* und *b* wurden nicht untersucht. Fraktion *c* erwies sich als angereichert an Keton VII, $n = 14$, während *d* nahezu reines IX, $n = 14$ enthielt. Diese Konstitutionszuweisung wurde durch Ferricyanid-Oxydation von *c* und *d* belegt. Ein Teil des 1,7-*Ketons* VII, $n = 14$ konnte kristallin erhalten werden: Nach Umlösen aus Petroläther (40–50°) farblose Blättchen vom Schmp. 107–107,8°.

Die angereicherte Fraktion wie auch das kristallisierte Keton VII, $n = 14$ gaben das gleiche 2,4-*Dinitrophenyl-hydrazon:* Aus Benzol-Alkohol ziegelrote Nadeln vom Schmp. 269° u.Z.

$C_{26}H_{28}O_4N_4$	(460,52)	Ber.	C	67,81	H 6,13
		Gef.	C	67,86	H 6,18

Die UV-Absorption entspricht mit Maxima λ_1 und $\lambda_2 = 240$ und 386 mμ und $\epsilon_1 = 34\,700$, $\epsilon_2 = 35\,300$ der Erwartung für das Derivat von VII, $n = 14$.

Aus der Fraktion *d* wurde das 2,4-*Dinitrophenyl-hydrazon* von IX, $n = 14$ erhalten; auch die Mutterlauge des oben beschriebenen Hydrazons erlaubte die Isolierung der gelben Nadeln, die nach Umlösen aus Methanol bei 162,0–163,5° schmolzen.

$C_{26}H_{28}O_4N_4$	(460,52)	Ber.	C	67,81	H 6,13
		Gef.	C	68,12	H 6,34

Die Lichtabsorption mit Hydrazonbande bei 365 mμ und $\epsilon = 24\,800$ ist die eines 2,4-Dinitrophenyl-hydrazons ohne Arylkonjugation. Auch die auf das 1-Alkyl-naphthalin-System zurückgehende Bande bei 230 mμ mit $\epsilon = 86\,100$ spricht für vollständige Entkoppelung. Das 2,4-Dinitrophenyl-hydrazon des analogen Ringketons II, $n = 14$ der Benzolreihe ist mit λ(Max.) = 368 mμ und $\epsilon = 26\,000$ ebenfalls völlig mesomeriegehindert.[2]

Oxim und Semicarbazon des Ketons IX, $n = 14$ konnten nicht erhalten werden.

Der *Deutschen Forschungsgemeinschaft* und dem *Fonds der Chemie* schulden wir Dank für die Förderung dieser Arbeit. Herrn Prof. Dr. W. Reppe, Badische Anilin- und Sodafabrik, sei für die Ueberlassung von Korksäure gedankt. Herr Dr. H. Hunsdiecker, Köln-Braunsfeld stellte uns dankenswerterweise Thapsiasäure-halbester zur Verfügung. Herrn Prof. F. Richter, Beilstein-Institut, danken wir für Ratschläge in Nomenklaturfragen.

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OXIDATIONS WITH COPPER–AMINE COMPLEXES—VI[1]*

OXIDATION OF AROMATIC AMINES AND OF ANILINE IN PARTICULAR

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Abstract—Aniline—in alcoholic solutions—was found to undergo *ortho*-oxidation by oxygen under the catalytic influence of (complexes containing) copper ions. The reaction shows analogy, but also some characteristic differences, with the catalytic *ortho*-oxidation reactions of phenols studied previously. The products were 2-amino-5-anilino-quinone-4-anil (70%), azobenzene (19%) and 3-aminophenoxazone (5%). A fourth, as yet unidentified, component was isolated by chromatography over Al_2O_3. The scope of the reaction and the influence of substituents were studied. Possible reaction mechanisms are considered.

In previous investigations on the conversion of phenols into orthoquinone derivatives with oxygen as an oxidant and copper–amine complexes as catalysts, Brackman and

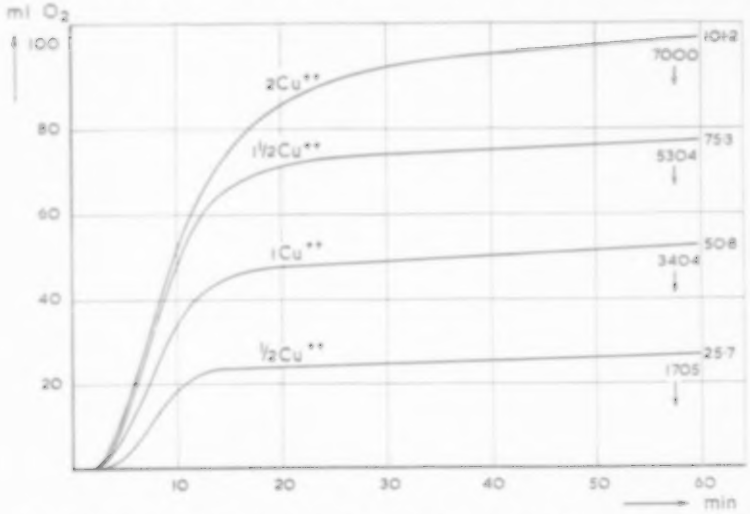

Fig. 1. Oxygen uptake as a function of time for solutions of 0·01 mole of aniline in 20 ml methanol with ½, 1, 1½ and 2 mmoles of cupric acetate. 0·1705, 0·3404, 0·5304 and 0·7000 g of copper complex precipitated in the four experiments enumerated.

Havinga used morpholine for complex formation on account of its stability, its relatively low volatility and its solubility in most media.[2] Extending the research it was found that primary aromatic amines were capable of rapid reaction with oxygen in presence of copper complexes. The results obtained with aniline are described in this paper.

The reactions were performed at room temperature under continuous magnetic stirring in the gas/liquid reaction apparatus described previously,[2] using methanol or

* Preceding paper of this series: W. Brackman and E. Havinga *Rec. Trav. Chim.* **74**, 1107 (1955).

[1] G. Engelsma Thesis, Leiden. To be published.
[2] W. Brackman and E. Havinga *Rec. Trav. Chim.* **74**, 937 (1955).

ethanol as solvent and commercial oxygen as oxidising agent. The copper–amine complex is first allowed to form in the evacuated apparatus, oxygen is then admitted from the gas burette. A precipitate of oxidation products soon forms.

The course of the reaction can be seen from Fig. 1, in which the oxygen uptake is plotted as a function of time for 0·01 mole of aniline in 20 ml of methanol and varying amounts of copper acetate. The oxygen uptake ends rather abruptly, the amount of reaction product (copper complexes) precipitated as well as the amount of oxygen consumed being practically proportional to the amount of copper acetate originally added. Addition of another portion of copper acetate causes the reaction to continue until eventually the aniline has completely been consumed.

The main reaction products were 2-amino-5-anilino-quinone-4-anil, azobenzene and 3-aminophenoxazone-2.* The amount of oxygen consumed corresponds with that calculated on the basis of the reactions leading to these products (cf. Experimental).

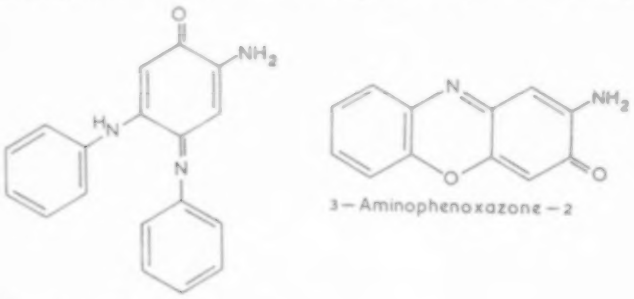

FIG. 2. Products isolated after catalytic autoxidation of aniline.

The reaction mixtures were analysed by separation of the precipitate from the mother liquor and subsequent extraction of the precipitate with ethanol. The liquid and the alcohol extracts contain azobenzene. The copper containing precipitate proved to be rather refractory to the usual methods of analysis but could be worked up by treating with ethanol which had been saturated with oxalic acid (some copper oxalate precipitates) and pouring the solution into ice-chilled dilute ammonia. The solid which separated was washed with water and crystallised from 70% ethanol, yielding a product identical with the substance obtained by oxidation of aniline with $NaBrO_3$ according to Majima.[3] Its constitution was proved to be 2-amino-5-anilino-quinone-4-anil and not the isomeride 2-anilino-5-amino-quinone-4-anil, a problem still unsolved after the investigation of Majima.

Condensation of both our product and of the compound obtained from bromate oxidation afforded a phenazine that proved to be identical with 2:3-dianilino-phenazine. The latter compound had been prepared from 3,4-dianilino-*o*-quinone and *o*-phenylenediamine according to the directions of Kehrmann and Cordone.[4] Moreover, it proved possible to obtain the 2-amino-5-anilino-quinone-4-anil by oxidation of *o*-aminophenol with silver acetate in the presence of two moles of aniline.

* A fourth, as yet unidentified, compound could be isolated in minute quantities from the reaction mixtures by chromatography.

[3] R. Majima *Ber. Dtsch. Chem. Ges.* **44**, 231 (1911).

[4] F. Kehrmann and M. Cordone *Ber. Dtsch. Chem. Ges.* **46**, 3011 (1913).

On extraction with ether the filtrate and washing liquids from the treatment of the copper containing precipitate with the ethanolic oxalic acid solution etc. yield the poorly water-soluble 3-amino-phenoxazone-2. This could easily be identified as it is the main product obtained upon oxidation of *o*-aminophenol by HgO [5] or by air.[6]*

Although full details of the mechanism of the catalytic aniline oxidation will be discussed in subsequent papers, we wish to communicate some suggestive data:

(1) Anilines having one or more methyl- or methoxy-substituents, as a rule are subject to rapid oxidation; anilines having a group *ortho*-substituted, however, are very slowly oxidised: it was observed that *m*-and *p*-toluidine, 3,4- and 3,5-dimethylaniline, *m*- and *p*-anisidine and *β*-naphthylamine reacted very rapidly while the rate of oxidation reaction for *o*-toluidine, *o*-anisidine, 2:4-di-methylaniline and *α*-naphthylamine is very low. Electron withdrawing substituents seem to have an inhibitory effect: *m*-chloro- and *m*-bromo-anilines were found to react very slowly; *o*- and *p*-chloroaniline, *o*- and *p*-bromoaniline and the three nitroanilines were not oxidised.

(2) The products isolated suggest that *o*-aminophenol or the corresponding semiquinone is an intermediate in the copper-catalysed oxidation of aniline.

(3) In addition to the oxidation, in which aniline is the only amine present, a copper-catalysed oxidation of aniline takes place in the presence of an excess of a primary or secondary aliphatic amine to yield other, partly unknown products. Whether this reaction is analogous to the oxidation of phenol catalysed by a copper–amine complex,† is being investigated.

(4) In the presence of cupric acetate, aniline and substituted anilines—even the nitroanilines and N-dimethylaniline—are oxidised very rapidly with H_2O_2. In the case of aniline and *p*-toluidine this reaction gives rise to the same products as the oxidation with oxygen mentioned above. In this connexion it may be mentioned that Mann and Saunders[7] also isolated azobenzene and 2-amino-5-anilino-quinone-4-anil from the oxidation of aniline with H_2O_2 in the presence of $FeSO_4$.

(5) Just as with the phenol oxidation a metal ion that can replace the copper ion in the aniline oxidation, was not found. The rate of the copper-catalysed reaction, however, is considerably increased by addition of Ni^{2+} or Co^{2+}. It may be remarked that both Co^{2+} and Ni^{2+} salts catalyse an oxidation reaction of aniline with H_2O_2, whereas Co^{2+} salts also play the role of catalysts in a reaction of *o*-aminophenol with a primary or secondary amine in the presence of oxygen. These reactions lead to different products, however, the structures of which have not yet been elucidated. The catalysed aniline oxidation is different from the phenol oxidation since the anion also exerts its influence: chloride, bromide and iodide, even in small quantities, are inhibitors. Nitrate, on the other hand, has an accelerating activity. When cupric nitrate instead of cupric acetate is used for the aniline oxidation, the total oxygen uptake increases and the black copper complex arising from this reaction, mainly consists of a still unknown quinonoid compound.

* The oxidation of *o*-aminophenol by air was found to be strongly catalysed by copper acetate. Normally this reaction is inhibited by the precipitation of a copper complex. This difficulty, however, could be overcome by adding drop-wise a solution of *o*-aminophenol to a solution of copper acetate pyridine complex in ethanol at such a rate that the oxidation was finished before the aminophenol–copper complex starts precipitating.

† See papers I–V of this series.

[5] O. Fischer and O. Jones *Ber. Dtsch. Chem. Ges.* **27**, 2784 (1894).

[6] F. Kehrmann *Ber. Dtsch. Chem. Ges.* **39**, 135 (1906).

[7] P. J. G. Mann and B. C. Saunders *Proc. Roy. Soc.* B **119**, 58 (1935).

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(6) Methanol and ethanol were found to be suitable solvents. In ethyl acetate, dioxane and benzene no reaction was observed.

(7) H_2O_2 reduces the induction time to zero. This is also effected by *o*-aminophenol and analogous compounds, such as *p*-aminophenol, pyrocatechol, hydroquinone, *o*- and *p*-phenylenediamine.

(8) The cuprous ion is probably involved in the reaction mechanism: on addition of cuprous acetate no induction time is observed. The same effect is brought about by addition of a few reducing agents which bear no structural relationships to *o*-aminophenol (phenylhydrazine, semicarbazide, ascorbic acid, $FeSO_4$).

As mentioned above, the *o*- and *p*-halogen-anilines cannot be oxidised under the same conditions as aniline. Addition of small amounts of hydrazine to the system, however, results in oxidation of the aniline component, giving the azobenzene derivative and quinonoid compounds.

For comparison, measurements with O_2–N_2 and O_2–CO mixtures were carried out and with the latter mixtures a considerable increase of the induction time and a lowering of the rate of oxygen uptake occurred which is in contrast with the phenomena observed with the phenol oxidation.

From the nature of the products isolated, the data on the course of the reaction and the effect of compounds added it may be concluded that the following reactions are of primary importance in the aniline oxidation.

(a) The introduction of oxygen at the *ortho*-position of aniline, taking place in an aniline–copper peroxide complex. For this reaction analogy is to be expected with the mechanism of the ortho oxidation of phenol as given in paper V of this series.[1] Some differences, however, seem to exist as evidenced by the sensitivity of the aniline oxidation towards carbon monoxide as well as to the presence of some ions (cf. 5).

(b) A series of oxidation and addition reactions of *o*-aminophenol (or of one of its oxidation products) with two equivalents of aniline, yielding amino-anilinoquinone-anil. Also oxidation and addition reactions of *o*-aminophenol to 3-aminophenoxazone-2 occur. With these reactions H_2O_2 or a copper peroxide complex may be formed, which affects reaction (a).

(c) Oxidation of aniline to azobenzene. This reaction is catalysed by an aniline–copper–oxygen complex (c.f. Terentiev and Mogilyanskii[8]).

EXPERIMENTAL*

Oxidation of aniline. The reaction mixture, consisting of aniline (9·3 g 0·1 mole), cupric acetate, 1 H_2O p.a. (6·0 g 0·03 mole) and methanol (200 ml), is placed in a reaction vessel as described previously[1] and stirred magnetically. The temperature being kept at 20°C, the reaction is finished within 2½ hr. The total of O_2 consumed amounts to 1560 ml (772·5 mm Hg, 20°C). The precipitate formed is filtered off and repeatedly washed with water or dilute ammonia to remove the unreacted cupric acetate. The substance is extracted with ethanol of 40°C till the solvent is colourless. Yield, 10·3 g of a black copper complex.

Azobenzene. The mother liquor and the washings are evaporated to dryness *in vacuo*. The residue consists mainly of azobenzene. On extraction with dilute

* The micro-analyses are by Mr. Han Kong Wan of our laboratory. Melting points are uncorrected.

[8] A. P. Terentiev and Ya. P. Mogilyanskii *Dokl. Akad. Nauk. SSSR (C.R. Acad. Sci., U.R.S.S.)* **103**, 91–3 (1955).

ammonia and crystallisation from 70% ethanol a pure product is obtained. During the oxidation of concentrated solutions of aniline as described above, a small amount of tarry by-products usually forms, from which azobenzene is purified by stream distillation or sublimation. Identification: spectrum and mixed melting point. Yield of crude product, 1·7 g; of pure substance, 1·2 g (13%). Found: C, 78·9; H, 5·8; N, 15·6. Calc. for $C_{12}H_{10}N_2$ C, 79·2; H, 5·5; N, 15·4%.

The black-copper complex. This complex is insoluble in organic solvents. It is sparingly soluble in dilute H_2SO_4 and HCl; the yellow-green colour of the solution turns red-violet via orange-red, indicating a rapid conversion (hydrolysis). The complex is less subject to chemical change when it is dissolved in ethanol to which concentrated H_2SO_4, dry HCl gas or a strong organic acid has been added. From the analysis no definite conclusions as to the composition of the black complex can be drawn. The results suggest that there is a 1:1 ratio of copper atoms to molecules of oxidation products. Found: N, 10·56; Cu, 17·34; N/Cu = 2·77. Calc. for N/Cu: 2·91.

The copper can be removed in the following way. To a solution of oxalic acid·$2H_2O$ (95 g) in ethanol (400 ml) copper complex (10·3 g) is added. A copper oxalate precipitate forms, which may be filtered. As soon as the original complex has disappeared, the solution (with or without precipitate) is poured into water (2·5 l.), to which ice (500 g) and concentrated ammonia (130 ml) have been added. The copper remains in solution and the organic substance, which precipitates almost quantitatively, forms red-brown cyrstals, mainly consisting of amino-anilino-quinone-anil.

2-*amino*-5-*anilino*-*quinone*-4-*anil*. In order to remove 3-amino-phenoxazone-2 the product is washed with water (20–30°C) until the washings are colourless. A pure product crystallises from 65% ethanol in rosettes of small brown-red needles, m.p. 127–128°. The same crystals form from a solution of the product in petroleum–ether (b.p. 80–100°). At room temperature pink needles, probably containing solvent, are deposited from the latter solution. Yield of the crude product, 6·8 g of pure substance, 6·0 g (63%). Found for the product of m.p. 127–128° N, 14·23. Calc. for $C_{18}H_{15}N_3O$: N, 14·44%.

Freshly prepared amino-anilino-quinone-anil gives a green solution in concentrated H_2SO_4; on standing for 15 min the solution becomes dichroic. The above characteristics, the values of the R_F with paper chromatography and the mixed melting point showed that our product is identical with a compound obtained from aniline by oxidation with $NaBrO_3$ according to the directions of Majima.[3] Starting from both products 2:3-dianilinophenazine was prepared.

2:3-*Dianilinophenazine*. A solution of amino-anilino-quinone-anil (1 g), *o*-phenylene-diamine (0·4 g) and glacial acetic acid (20 g) in ethanol (30 ml) is boiled for 3 hr under reflux. On cooling, the reaction mixture is poured into dilute ammonia (200 ml); an orange-yellow precipitate forms. Crystallisation from 95% ethanol yields shining orange leaflets of 2:3-dianilino-phenazine·1 mole ethanol, m.p. 220–221° (cf. Kehrmann and Cordone, m.p. 218–219°). The violet colour of a solution of the crystals in concentrated H_2SO_4 becomes red-violet on diluting with H_2O. The mixed melting point indicates that the product is identical with the dianilino-phenazine synthesised according to the directions of Kehrmann and Cordone[4] from 4:5-dianilino-*o*-quinone and *o*-phenylene-diamine. Found: N, 15·33. Calc. for $C_{24}H_{18}N_4$: N, 15·43%

3-*Amino-phenoxazone*-2. On extraction of the filtrate and the washings obtained from the crude amino-anilino-quinone monoanil (see above) with ether, evaporation

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of the ether and crystallisation of the residue from 80% ethanol, gave 3-amino-phenoxazone-2 (needles or leaves containing 1 mole of alcohol of crystallisation). This compound proved to be identical with the product prepared according to the directions of Fischer and Jonas[5] by oxidation of *o*-aminophenol with HgO as well as with the product obtained from catalytic oxidation of *o*-amino-phenol (identical R_F values with chromatography, spectra, no depression of the mixed melting point). The pure substance melts at 249–250°. The solution in concentrated H_2SO_4 has a violet colour, turning red on addition of water. Found: N, 10·95. Calc. for $C_{12}H_8N_2O_2 \cdot C_2H_6O$: N, 10·85%. Found: N, 13·13. Calc. for $C_{12}H_8N_2O_2$: N, 13·20%.

Synthesis of 2-amino-5-anilino-quinone-4-anil. The anil was synthesised in a way analogous to the one described for the preparation of 4:5-dianilino-*o*-quinone by Kehrmann and Cordone.[4] With continuous stirring AgO (6·4 g) is added to glacial acetic acid (200 ml) and when all AgO has disappeared, *o*-aminophenol (2·0 g) and aniline (4·0 g) are added simultaneously. The reaction mixture becomes brown-red and Ag deposits. After standing for 15 min the Ag is filtered off and the filtrate is poured into excess of dilute ammonia. The precipitate mainly contains amino-anilino-quinone monoanil and a small amount of 3-amino-phenoxazone-2. The latter is removed by washing with water. The crude amino-anilino-quinone anil is crystallised from 70% ethanol; yield, 4·0 g (75%).

Fourth component. A minute amount of a fourth component is isolated on chromatographic separation of the organic substances forming the copper complex (see below). This compound dissolves in warm ethanol with an orange-yellow colour. On cooling, orange needles, m.p. 158–159°, are deposited. In concentrated H_2SO_4 the compound has a violet colour, turning red on addition of water.

Balance. With the catalytic oxidation of aniline (0·1 mole) described above the following crude products were found: amino-anilino-quinone anil (0·023[5] mole), azobenzene (0·009[5] mole) and 3-amino-phenoxazone-2 (0·002[5] mole). For the formation of these products 0·070,[5] 0·019, 0·005 mole of aniline and 0·047, 0·009,[5] 0·006 mole of O_2 are required. Thus, 94% of the aniline appears to have been converted into the three products enumerated, while the amount of oxygen consumed (0·064[5] mole) is in agreement with the calculated amount (0·062[5] mole). Oxidation of methanol to formaldehyde and formic acid occurred since the specific odour of these compounds was observed.

Chromatography. On separation of the copper-free reaction mixture on a column of Al_2O_3 with 80% *cyclo*hexane—20% dioxane as an eluent the following bands appear in order of decreasing mobility:

Band colour	Type	Colour solution in conc. H_2SO_4 Colour solution on addition of H_2O	Compound
1. Yellow	broad	yellow	azobenzene
2. Yellow	narrow	violet/red	unidentified
3. Orange-yellow	narrow	violet/red	3-amino-phenoxazone-2
4. Red	broad	green/red-violet	amino-anilino-quinone anil
5. Brown-black	narrow	—	tarry by-product

With circular paper chromatography the best results were obtained when using 80% methanol—20% water as stationary phase and *cyclo*hexane as eluent. Paper: Whatman no. 1. Colouring of the spots corresponding with the quinonoid compounds was increased by HCl vapour.

Acknowledgement—The co-operation and discussions with Mr. E. Th. Mulder, who will continue the investigations along certain lines indicated in this paper, is gratefully acknowledged.

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ON ISOMERISATION OF NITROPARAFFINS

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(*Received* 4 *October* 1957)

Abstract—The investigation deals with the isomerisation of primary nitroparaffins into hydroxamic acids under influence of acetic anhydride or ketene, in presence of basic catalysts.

A practical application of the hydrolysis of 1:2-dinitroethane to hydroxylamine sulphate is described.

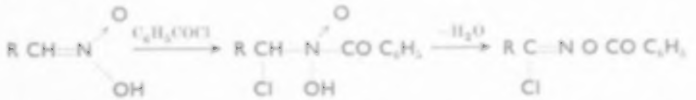
Another application is the preparation of caprolactam by the reaction of *cyclo*hexanone with 1:2-dinitroethane in presence of concentrated sulphuric acid.

INTRODUCTION

IT is well known, that primary nitroparaffins can be hydrolysed to hydroxylamine.[1,2] Bamberger and Rüst[3] elucidated the mechanism of this reaction. They showed that primary nitroparaffins are isomerised in acid medium into hydroxamic acids and the latter can be hydrolysed to carboxylic acids and hydroxylamine.

Geuther[4] attempted to explain the mechanism of formation of hydroxylamine from primary nitroparaffins by ascribing them a structure of "amidoxydes". Taking into account the German terminology, this might signify "hydroxyamide" which is one of the desmotropic forms of hydroxamic acids. Also it would be interesting to point out that a number of authors[5,6,7] prior to Bamberger, found that a relation exists between primary nitroparaffins and hydroxamic acids, namely, that acid chlorides can react with sodium salts of *aci*-nitroparaffins yielding mono- or di-acylderivatives of hydroxamic chlorides.

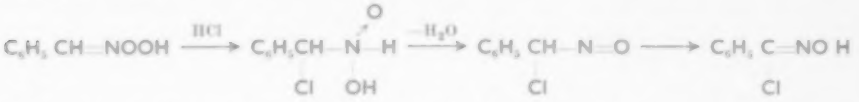
This reaction was investigated by Wieland and Kitasato.[8] They treated *aci*-nitroparaffins with acid chlorides in presence of pyridine and suggested that the mechanism of the reaction consists in adding acid chloride to the double bond of the aciform of nitroparaffins. The additive compound then loses water and acylhydroxamic chloride results:



Nenitzescu and Isacescu[9] also investigated this reaction, and found that the mechanism suggested by Wieland and Kitasato occurred when anhydrous HCl reacted with

[1] R. Preibisch *J. Prakt. Chem.* **7**, 480 (1873).
[2] V. Meyer *Ber. Dtsch. Chem. Ges.* **8**, 29 (1875); V. Meyer and J. Locher *Liebigs Ann.* **180**, 163 (1876).
[3] E. Bamberger and E. Rüst *Ber. Dtsch. Chem. Ges.* **35**, 45 (1902).
[4] A. Geuther *Ber. Dtsch. Chem. Ges.* **7**, 1620 (1874).
[5] J. U. Nef *Ber. Dtsch. Chem. Ges.* **29**, 1218 (1896).
[6] A. T. Holleman *Rec. Trav. Chim. Pays-Bas* **15**, 356 (1896).
[7] A. van Raalte *Rec. Trav. Chim. Pays-Bas* **18**, 378 (1898).
[8] H. Wieland and Z. Kitasato *Ber. Dtsch. Chem. Ges.* **62**, 1250 (1929).
[9] C. D. Nenitzescu and D. A. Isacescu *Bull. Soc. Chim. Roumanie* **14**, 53 (1932).

phenyl-*aci*-nitromethane. An additive compound was first formed, and after losing water it was transformed into a blue nitroso compound which was isomerised to benzohydroxamic chloride:



Primary *aci*-nitroparaffins react with acid chlorides in the same way as indicated by Wieland. However, when sodium salts of *aci*-nitroparaffins were used, acyl derivatives of hydroxamic acids resulted:

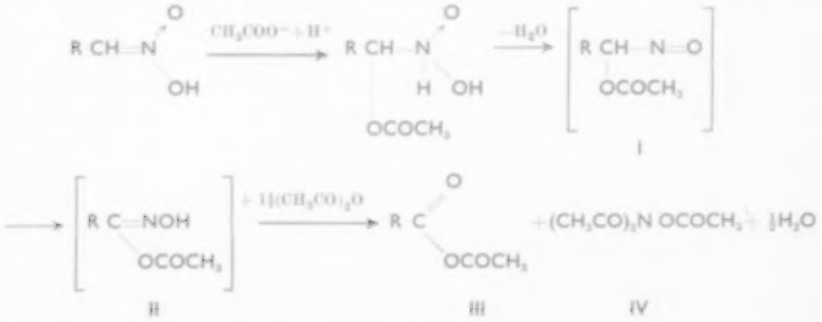
Further experiments on formation of hydroxamic acids from primary nitroparaffins were carried out by Melnikov[10] who confirmed the earlier statement by Geuther[4] that ammonium salts are also formed in addition to hydroxylamine.

Junell[11] examined the kinetics of transformation of nitroethane into acethydroxamic acid and found it to be a reaction of the first order. Lippincott and Haas[12] investigated the conditions of hydrolysis of primary nitroparaffins and determined the yield of hydroxylamine (86–91 per cent), ammonia (6–7 per cent) and carboxylic acids (90–96 per cent).

Using the fact that primary nitroparaffins furnish hydroxylamine, Turski[13] worked out new conditions for his reaction of direct amination of aromatic compounds.[14]

The author of the present paper also investigated[15] the isomerisation of primary nitroparaffins using acetic anhydride in presence of basic agents such as sodium acetate or pyridine. The presence of a basic agent is essential, the reaction does not occur without it. This indicates that the *aci*-form is an intermediate in formation of the final product, which is diacetylacethydroxamic acid, or O,N,N-triacetylhydroxylamine (IV).

The author suggested a mechanism similar to that of Wieland[8] or Nenitzescu:[9]



[10] N. V. Melnikov *J. Gen. Chem., Moscow* **4**, 1061 (1934).
[11] R. Junell *Ark. Kemi. Min. Geol.* B **11**, No 30 (1934).
[12] S. B. Lippincott and H. B. Haas *Industr. Engng. Chem.* (*Industr.*) **31**, 118 (1939).
[13] J. S. Turski *Brit. Pat.* 564 610 (1944); *U.S. Pat.* 2 401 525 (1946).
[14] J. S. Turski *Ger. Pat.* 287 756 (1915).
[15] T. Urbański *J. Chem. Soc.* 3374 (1949).

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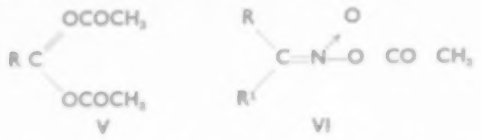
The blue intermediate is probably a nitroso compound (I), which would isomerise to another hypothetical intermediate—II. Acetolysis of (II) would yield an anhydride (III), and the final compound (IV).

Urbański and Gurzyńska[16] investigated also the action of ketene on primary nitroparaffins. The reaction also takes place in presence of basic agents, but it is evidently milder, than with acetic anhydride.

Thus, the hypothetical intermediate compound (II) was subjected to acetylation, the diacetyl derivative (V) of hydroxamic acid being formed:



V VI

By acting on secondary nitroparaffins with acetic anhydride or ketene, in presence of sodium acetate, an acetyl derivative of *aci*-form (VI) was obtained. It can also be considered as a mixed anhydride of acetic anhydride and *aci*-nitroparaffin.

It should be pointed out, that Nenitzescu and Isacescu[9] tried to act with ketene on primary nitroparaffins. They obtained a definite compound—acetylbenzohydroxamic acid—only in the case of *aci*-phenylnitromethane. Other nitroparaffins did not furnish definite compounds.

EXPERIMENTAL

Isomerisation and hydrolysis of 1:2-*dinitroethane*

1:2-Dinitroethane is the cheapest among primary nitroparaffins. It can easily be prepared as described by Levy, Scaife and Smith[17] who investigated the hydrolysis of dinitroethane with hydrochloric acid, and the yield of hydroxylamine hydrochloride which remained in solution was found to be 90·8 per cent of theoretical.

The author of the present paper in collaboration with T. Dobosz carried out a number of experiments using 1:2-dinitroethane as a starting material to produce hydroxylamine salts. Experiments by Levy *et al.* have been repeated. Hydrolysis of slightly larger quantities of dinitroethane (e.g. 2 g) with hydrochloric acid led to vigorous reaction accompanied by a considerable increase of pressure owing to decomposition of oxalic acid formed in the reaction.

Better results have been obtained when concentrated sulphuric acid was used, 2 mol. for 1 mol. of dinitroethane. The reaction was carried out in an open vessel at 100°.

The reaction is vigorous and to moderate it, dinitroethane was dissolved in glacial acetic acid, e.g. in the ratio 50 : 50 prior to introduction into sulphuric acid. The acetic acid can be recovered by increasing the temperature to 120° at the end of the reaction.

Hydroxylamine sulphate $(NH_2OH)_2 \cdot H_2SO_4$ was isolated in a crystalline form with a yield of 75–79 per cent.

When sulphuric acid of lower concentration was used, the reaction was slow and required a higher temperature. The yield was lower.

Oxalic acid could not be isolated from the reaction since most of it was decomposed during the reaction.

[16] T. Urbański and W. Gurzyńska *Roczn. Chem.* **25**, 213 (1951).
[17] N. Levy, C. W. Scaife and A. E. Wilder Smith *J. Chem. Soc.* 1096 (1946).

A patent was obtained[18] for the preparation of hydroxylamine sulphate from 1:2-dinitroethane.

Preparation of caprolactam from cyclo*hexanone and* 1:2*-dinitroethane*

Novotný[19] suggested a new method of preparing caprolactam, which consists in warming a solution of *cyclo*hexanone and a primary nitroparaffin in concentrated sulphuric acid. This method was examined and confirmed by Piotrowski[20]—one of the present authors' collaborators.

In collaboration with Piotrowski a possibility of using 1:2-dinitroethane as primary nitroparaffin was now examined. Dinitroethane dissolved in glacial acetic acid was introduced into concentrated sulphuric acid at 120°, and *cyclo*hexanone was then introduced into the solution. Acetic acid was distilled and after cooling caprolactam separated. The yield was ca. 72 per cent calculated on *cyclo*hexanone used.

A patent was obtained for this reaction.[21]

Preparation of hydroxylamine sulphate

Two grammes of 1:2-dinitroethane was added in small portions to 3·5 g of concentrated sulphuric acid (98 per cent) previously heated to 100°C and stirred. The reaction was very vigorous due to decomposition of oxalic acid formed during the reaction.

The reaction mixture was cooled below room temperature (5–10°C) and 8–10 ml of ethyl alcohol was added. A precipitate of hydroxylamine sulphate was filtered, washed with alcohol and ether. The yield was 2·13 g (79 per cent of theoretical).

Preparation of caprolactam

Ten grammes of 1:2-dinitroethane was dissolved in an equal weight of glacial acetic acid. The solution was introduced dropwise during 20 min into 35 g of concentrated sulphuric acid, the temperature being maintained between 120–125°C. The reaction flask was kept in a bath of calcium chloride solution boiling at 120°.

*Cyclo*hexanone (12·5 mg) was added dropwise during 24 min to the reaction mixture, the temperature being still kept at 120°.

Acetic acid was removed by distillation.

After the reaction was completed (this was marked by a fall of temperature in the reaction flask), the reaction mixture was carefully neutralised by introducing it into cold aqueous 25% solution of ammonia, the temperature being kept below 50°. The mixture separated into two layers, the lower one consisted of a saturated aqueous solution of ammonium sulphate, the upper layer consisted of caprolactam, which was dissolved in ether, dried over anhydrous sodium sulphate, and purified by distillation b.p. 138–9°/11–12 mm Hg.

The yield was 10·5 g of caprolactam, i.e. ca. 72 per cent (calculated on *cyclo*hexanone).

Acknowledgements—The author thanks Mr. T. Dobosz and Mr. A. Piotrowski for carrying out experiments with 1:2-dinitroethane.

[18] T. Urbański and T. Dobosz *Polish Pat.* 40008 (1956).
[19] A. Novotný *Swiss Pat.* 273402 (1952); *U.S. Pat.* 2 569 114 (1952); A. Stoy and A. Novotný *Nova Syntetická Vlákna.* Statní Nakladatelstvi Technické Literatury, Prague (1953).
[20] A. Piotrowski *Przem. Chem.* **12,** 405 (1956).
[21] T. Urbański and A. Piotrowski *Polish Pat.* 40009 (1956).

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SOME REMARKS ON THE THEORY OF NITRATION

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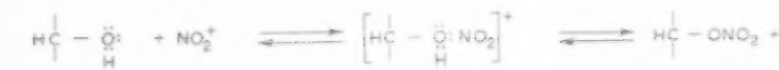
(*Received* 15 *July* 1957)

Abstract—Experiments on formation of nitric esters of starch ("O-nitration" of starch) led to the conclusion, that nitration occurs not necessarily by means of NO_2^+ ions, but NO_3^- ions and/or undissociated nitric acid are nitrating agents.

Nitrating mixtures rich in nitric acid may yield products of higher nitrogen content owing to the fact that the reaction occurs in one phase system.

THE excellent review by Gillespie and Millen[1] which was partly based on the extensive work of Ingold and his school published later[2] gave a first summary of the present state of our knowledge on the nature of nitration agents and particularly on the role of nitronium ion in aromatic nitration

So far not very much attention had been paid to the role of nitronium ion in the nitration of hydroxyl compounds, i.e. in the formation of O-nitro compounds. The only note is by Israelashvili[3] and in it he suggested that the formation of the nitrates is due to an attack of the nitronium ion on a lone electron pair of the hydroxyl oxygen followed by elimination of a proton from the transient intermediate product:



However, according to Miles[4] it is not necessary to assume that NO_2^+ ion plays any part in the esterification of cellulose and there are two very strong reasons to believe that in the greater part of the cellulose "nitration field" it cannot have any effect.

According to Miles one of the proofs is the fact that nitration can take place in the vapour of nitric acid at very low pressure when no liquid can be present and the formation of NO_2^+ or any other ion is most improbable.

Another one is the possible nitration of cellulose by means of dilute nitration mixtures which do not contain spectroscopically detectable NO_2^+.[5]

Again according to Miles the modern work elaborates and confirms an old idea of Sapozhnikov[6] that the nitrating action of mixtures of nitric acid, sulphuric acid and water upon cellulose is related to the partial vapour-pressure of HNO_3 in the mixtures.

This theory was based on the similarity of the curves of constant nitrogen content of nitrocellulose and of constant vapour-pressure of HNO_3.

Sapozhnikov's work on the nitration of cellulose and on vapour-pressure was later repeated and confirmed by a number of authors.[7,8,9]

[1] R. J. Gillespie and D. J. Millen *Quart. Rev. Chem. Soc. Lond.* **2**, 277 (1948).
[2] C. K. Ingold *et al.* *J. Chem. Soc.* 2400–2678 (1950).
[3] Sh. Israelashvili *Nature, Lond.* **165**, 686 (1950).
[4] F. D. Miles *Cellulose Nitrate* p. 87. Oliver and Boyd, London–Edinburgh (1955).
[5] J. Chédin *Mém. Serv. Chim. de l'État* **31**, 113 (1944).
[6] A. Sapozhnikov *Z. phys. Chem.* **49**, 697 (1904); *Ibid.* **51**, 609 (1905); *Ibid.* **53**, 225 (1905); *Z. Ges. Schiess-U. Sprengstoffw.* **1**, 453 (1906); *Ibid.* **4**, 441 (1909).
[7] E. Berl and E. Berkenfeldt *Angew. Chem.* **41**, 130 (1928).
[8] F. G. Miles and M. Milbourn *J. Phys. Chem.* **34**, 2598 (1930).
[9] R. Vandoni *Mém. Serv. Chim. de l'État* **31**, 87 (1944).

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O-NITRATION OF STARCH*

The authors of the present paper carried out a number of experiments on O-nitration of starch and partly published their results between 1932 and 1939.[10]

The action of over 100 nitration mixtures of nitric acid, sulphuric acid and water was examined. The compositions varied within the ranges:

15–100 per cent HNO_3

0–75 per cent H_2SO_4

0–75 per cent H_2O

and the weight to weight ratio of starch to nitration mixture was 50. The temperature during the reaction was 10–12°C and the time 1 hr.

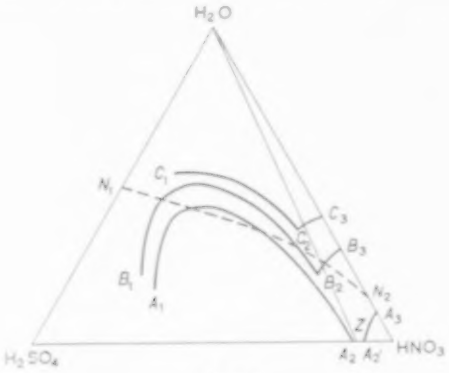

Fig. 1

The degree of O-nitration produced in our experiments is represented on the triangular diagram (Fig. 1), where the composition of the mixtures is expressed in molar percentages. The curves are formed by joining points corresponding to the composition of nitration mixtures yielding products of the same degree of nitration (constant nitrogen lines).

Thus, all nitrating agents with compositions lying on the curves A_1A_2 and $A_2'A_3$ give starch nitrates (which we shall call "nitrostarch") containing 12·75 per cent N. All mixtures lying between curve A_1A_2 and the baseline and between curve A'_2A_3 and the baseline give products with more than 12·75 per cent N.

The curves $B_1B_2B_3$ and $C_1C_2C_3$ correspond to nitration to 11·11 per cent and 9·15 per cent respectively. Mixtures with compositions between the curves A_1A_2–$A_2'A_3$ and $B_1B_2B_3$ give starch nitrates of nitrogen content between 12·75 and 11·11 per cent. Mixtures with compositions between $B_1B_2B_3$ and $C_1C_2C_3$ yield products with between 11·11 and 9·15 per cent N.

DISCUSSION

The curves A_1A_2, B_1B_2 and C_1C_2 are remarkably similar in shape to those given by Sapozhnikov[6] and others[7,8] for the nitration of cellulose.

* The authors suggest using the term "O-nitration" to denote the formation of nitric esters, by analogy with "N-nitration" and "C-nitration" to form nitramines and nitro-compounds respectively.

[10] J. Hackel and T. Urbański *Roczn. Chem.* **12**, 276 (1932); *Z. ges. Schiess-u. Sprengstoffw.* **28**, 306 (1933); *VI^e Congrès Intern. des Industries Agricoles* p. 766. Budapest (1939).

As with cellulose the region of mixtures which can O-nitrate starch evidently extends beyond that containing detectable concentrations of NO_2^+ ions which is bounded by the curve N_1N_2 according to Chédin[5] and Gillespie and Millen.

Thus nitronium ion cannot be considered as the only nitrating agent yielding O-nitro derivatives of starch—a statement analogous to that on cellulose nitration made by Miles.[4] It must be admitted therefore that nitric acid itself, probably in the undissociated form NO_2OH, and possibly also the nitrate ion NO_3^- are both O-nitrating agents for starch. Nevertheless it is mixtures rich in NO_2^+ ion which give nitrostarch of the highest degree of nitration and nitronium ions should still be considered as a most efficient nitrating agent.

In addition the rule of Sapozhnikov[6] on the importance of the vapour-pressure of HNO_3 seems to be confirmed by the general trend of the curves A_1A_2, B_1B_2 and C_1C_2.

However, the curve $A_2'A_3$ and the branches B_2B_3 and C_2C_3 show a definite deviation from the rule as established for the nitration of cellulose. The curves mentioned above lie between the H_2O–HNO_3 axis and the line H_2O—Z which represents mixtures with the HNO_3/H_2SO_4 ratio running from about 90/10 to 100/0.

It is evident that these mixtures have a relatively stronger nitrating action upon starch than upon cellulose.

An important property of all these nitrating mixtures is their ability to dissolve starch partly or totally. The higher the HNO_3/H_2SO_4 ratio in this region, the more completely soluble is the starch. This would account for the trend of the curves $A_2'A_3$, B_2B_3 and C_2C_3. The nitrogen content of the products also increases with increasing HNO_3/H_2SO_4 ratio.

The nitration of starch proceeds in this region in a system which is either completely single phase or partly so in contrast with cellulose, which swells only in mixtures rich in nitric acid and low in sulphuric acid. Swelling of cellulose hinders the uniformity of the process and makes the nitration even more difficult. Once more the importance of the effect of the factor of diffusion of nitrating mixture into the cellulose fibres upon the rate and degree of nitration can be pointed out. According to Sakurada[11,12] the kinetics of nitration of cellulose can be characterised by means of an equation:

$$x = k \cdot z^m$$

where: x is the weight of the product,
z is the time required for the reaction,
k and m are constants depending on the rate of diffusion of the acid into the fibres.

It is true that cellulose can also be dissolved in mixtures very rich in nitric acid but this requires a longer time and leads to marked degradation of the cellulose.

On the contrary starch is quickly dissolved in nitric acid or in the nitrating mixtures rich in nitric acid and can be isolated by pouring the solution into water.

SUMMARY

O-Nitration of starch was examined by means of nitrating mixtures composed of nitric acid, sulphuric acid and water and curves relating constant nitrogen content in the product to mixture composition were plotted on a triangular diagram.

[11] I. Sakurada *J. Soc. Chem. Ind., Japan* **35**, 123, 282 (1932); *Ibid.* **36**, 28, 299 (1933).
[12] I. Sakurada, T. Nakashima and H. Nakahara *J. Soc. Chem. Ind., Japan* **39**, 51 (1936).

The following conclusions can be drawn from the experiments:

(1) Starch, like cellulose, can be nitrated by relatively dilute nitrating mixtures which do not contain nitronium ions. This indicates that undissociated nitric acid (NO_2OH) and/or nitrate ion (NO_3^-) are also O-nitrating agents.

(2) The constant nitrogen curves all have two branches. The main branches follow remarkably well the trend of the Sapozhnikov curves established for the nitration of cellulose and for the partial vapour-pressure of HNO_3.

The shorter branches correspond to mixtures rich in nitric acid. Their nitrating action upon starch does not follow the rule of Sapozhnikov. This deviation is probably due to the ability of these mixtures to readily dissolve starch.

(3) The higher the HNO_3/H_2SO_4 ratio in the nitrating mixtures in the region from 90/10 to 100/0, the greater is the solvent power for starch and at any given HNO_3/H_2O ratio the higher is the nitrogen content of the product.

(4) Comparison of the action of mixtures rich in nitric acid upon cellulose and starch leads once more to the establishment of the importance in nitration of the factor of diffusion of the acids into the cellulose fibres.

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STEREOCHEMISTRY OF THE LITHIUM ALUMINUM DEUTERIDE REDUCTION OF THE THIIRANE RING*

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(*Received* 6 *November* 1957)

Abstract—Inversion of configuration has been demonstrated for the opening of the thiirane ring using lithium aluminum deuteride. This is based on a comparison of the optical activity of butane-2-D obtained from 2,3-dimethylthiirane with that from reductive displacement of other functional groups.

THE ready availability of optically active four-carbon compounds from a bacterial fermentation of carbohydrates[1] has resulted in a convenient series of compounds for the stereochemical evaluation of lithium aluminum deuteride reductions. The action of *Bacillus polymyxa* on glucose yields (RR)-2,3-butanediol† in a high state of optical purity. This, in turn, can be converted to (RR)-2,3-epoxybutane,[2,3] (R)-2-butanol,[4] (R)-2-methanesulfonoxybutane,[5] (S)-2-bromobutane,[6] and (SS)-2,3-dimethylthiirane,[7] all with established configuration.

With the exception of the alcohols mentioned above, the functional groups of these compounds can be replaced by deuterium using lithium aluminum deuteride, leading to butane-2-D from the aliphatic compounds, 2-butanol-3-D from the epoxide, and 2-butanethiol-3-D from the thiirane. Furthermore, the last two can be converted to butane-2-D by appropriate reductions. A measurable optical rotatory power for butane-2-D was predicted by Fickett[8] and subsequently verified experimentally.[9,10] The use of this property has been a convenient tool in comparing the steric route of reductions of the type in question.

The oxygen and sulfur heterocyclic compounds were carried through the reaction sequences shown in Fig. 1, so that introduction of the deuterium atom took place during ring opening.

The results of observations of the optical activity of the various butane-2-D samples are given in Table 1. In our previous studies[5,9] an absolute configuration was assigned to the butane-2-D isomers on the basis of three principal pieces of evidence: (1) *trans*-opening of the epoxide ring, using lithium aluminum hydride, was observed in the

* This work, and related work on deuteride reductions,[5,9] was supported by grants from Research Corporation.

† The configuration of optically active compounds is indicated by the (RS) method proposed by R. S. Cahn, C. K. Ingold and V. Prelog *Experientia* **12**, 81 (1956).

[1] D. Rose and S. King *Canad. J. Res.* **23F**, 79 (1945).
[2] H. J. Lucas and C. W. Gould, Jr. *J. Amer. Chem. Soc.* **63**, 2541 (1951).
[3] H. J. Lucas and H. K. Garner *J. Amer. Chem. Soc.* **70**, 990 (1948).
[4] P. J. Leroux and H. J. Lucas *J. Amer. Chem. Soc.* **73**, 41 (1951).
[5] G. K. Helmkamp and B. F. Rickborn *J. Org. Chem.* **22**, 479 (1957).
[6] P. A. Levene and R. E. Marker *J. Biol. Chem.* **91**, 405 (1931).
[7] C. C. Price and P. F. Kirk *J. Amer. Chem. Soc.* **75**, 2396 (1953).
[8] W. Fickett *J. Amer. Chem. Soc.* **74**, 4204 (1952).
[9] G. K. Helmkamp, C. D. Joel and H. Sharman *J. Org. Chem.* **21**, 844 (1956).
[10] A. F. LeC. Holding and W. A. Ross *Soc. Chem. Ind., Lond.* 1276 (1956).

bicyclic epoxides;[11] (2) second-order kinetic data was obtained for the reduction of primary alkyl bromides with the same reagent;[12] and, (3) the sign associated with the optical rotatory power of (R)-butane-2-D, as calculated by Fickett,[8] was positive. This indicates that dextrorotatory butane-2-D must be assigned the (R)-configuration. As indicated in Fig. 1, the successive reaction of (SS)-2,3-dimethylthiirane with lithium aluminum deuteride and Raney nickel led to dextrorotatory, hence (R), butane-2-D.

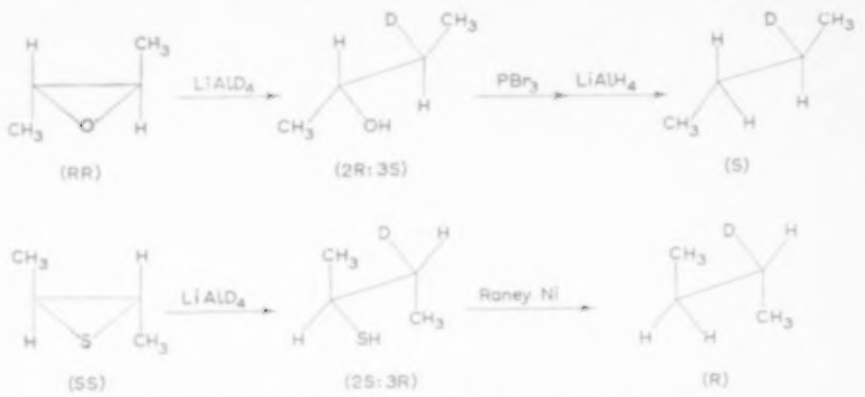

FIG. 1. Stereospecific introduction of deuterium by ring opening.

Consequently, ring opening was accompanied by inversion of configuration, and the (2S:3R) configuration must be assigned to the 2-butanethiol-3-D intermediate. Our interpretation is consistent with the observation of Bordwell *et al.*[13] that the ring of methylthiirane is opened at the 1-position with lithium aluminum hydride.

TABLE 1. OPTICAL ROTATION OF BUTANE-2-D OBTAINED BY VARIOUS LITHIUM ALUMINUM DEUTERIDE REDUCTIONS

Parent compound	Butane-2-D, $[\alpha]_D^{25}$
(RR)-2,3-Epoxybutane	−0·56°
(SS)-2,3-Dimethylthiirane	+0·36°
(R)-2-Methanesulfonoxybutane	−0·47°
(S)-2-Bromobutane	+0·50°

As in the case of the deuterobutanol, which was converted into (SR)- and (SS)-isomers of butane-2,3-D_2 (Fig. 2),[5] an attempt was made to convert (2S:3R)-2-butanethiol-3-D into butane-2,3-D_2. This proved unsuccessful, for deuteride reduction of the methanesulfonate ester of the thiol yielded mainly the original thiol, as reported for similar esters.[14] Also, it has been established that Raney nickel desulfurization is non-stereospecific for simple systems with no participating adjacent groups.[15]

[11] L. W. Trevoy and W. G. Brown *J. Amer. Chem. Soc.* **71**, 1675 (1949).
[12] D. J. Malter, J. H. Wotiz and C. A. Hollingsworth *J. Amer. Chem. Soc.* **78**, 1311 (1956).
[13] F. G. Bordwell, H. M. Andersen and B. M. Pitt *J. Amer. Chem. Soc.* **76**, 1082 (1954).
[14] J. Strating and H. J. Backer *Rec. Trav. Chim. Pays-Bas* **69**, 638 (1950).
[15] W. A. Bonner *J. Amer. Chem. Soc.* **74**, 1034 (1952).

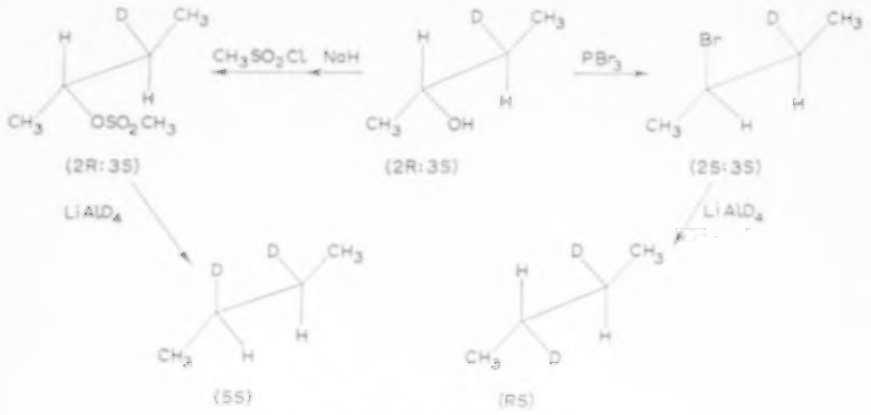

FIG. 2. Stereoisomers of butane-2,3-d_2.

EXPERIMENTAL RESULTS

(*RR*)-2,3-*epoxybutane*. The active epoxide was prepared by the procedure of Lucas *et al.*[2,3] from (RR)-2,3-butanediol.* The epoxide had $[\alpha]_D^{25}$ +57·2°, indicating an optical purity of 97 per cent based on the best previous value, +59·05°.[3]

(*SS*)-2,3-*dimethylthiirane*. This was prepared from the epoxide according to the thiourea method of Bordwell and Andersen.[16] Yield, 73 per cent; b.p. 88–89° (735 mm); n_D^{25} 1·4587; d_4^{25} 0·8863; MR_D, Calcd. 27·13, Found 27·08; $[\alpha]_D^{25}$ −129·0° (In reference 7 n_D^{25} 1·4390; $[\alpha]_D^{25}$ − 94·33°).

(2*S*:3*R*)-2-*butanethiol*-3-D. Reduction of the active thiirane was carried out in refluxing ethyl ether using a 1:1 molar ratio of lithium aluminum deuteride.[17] In preliminary studies, more efficient use of the reducing agent was sought by the use of lithium aluminum hydride and lithium hydride mixtures, but the advantages were doubtful. In all instances, with reaction times of up to 12 hr, the product was contaminated with starting material, and isolation required removal of the latter by

TABLE 2. PHYSICAL CONSTANTS OF BUTANETHIOLS

	(2S:3R)-2-Butanethiol-3-D	(SR)-2-Butanethiol	Literature
B.p	82–82·5° (735 mm)	83° (735 mm)	84–85°[18]
n_D^t	1·4303 (25°)	1·4302 (25°)	—
d_4^t	0·8277 (25°)	0·8185 (25°)	0·8299 (17°)[18]
d_4^{25}, calcd.[18]	0·8277	—	—
MR_D, Calcd., Found	28·37, 28·48	28·37, 28·47	—
$[\alpha]_D^t$,	+32·0° (25°)	—	+15·7° (20°)[20]

* The authors are indebted to Dr. R. W. Watson of the National Research Council of Canada for the culture of *Bacillus polymyxa* used in the biosynthesis of the diol.

[16] F. G. Bordwell and H. M. Andersen *J. Amer. Chem. Soc.* **75,** 4959 (1953).
[17] M. Mousseron, R. Jacquier, M. Mousseron Canet and R. Zagdoun *Bull. Soc. Chim. Fr.* 1042 (1952).
[18] A. McLean and R. Adams *J. Amer. Chem. Soc.* **58,** 804 (1935).
[19] S. Reymann *Ber. Dtsch. Chem. Ges.* **7,** 1287 (1874).
[20] P. A. Levene and L. A. Mideska *J. Biol. Chem.* **63,** 85 (1925).

extraction with pentane from an aqueous solution of potassium hydroxide. The yield of purified product was about 35 per cent.

(*R*)-*butane*-2-D. The reduction of the thiol was carried out with Raney nickel in refluxing ethanol.[21] From 3·4 g (0·037 mole) of the thiol was obtained 1·7 g butane-2-D in 7 hr: yield, 77 per cent; d_4^{25} 0·5856; α_D^{25} +0·21°; $[\alpha]_D^{25}$ +0·36° (Lit.: d_4^{25}, Calcd.,[18] 0·5836; $[\alpha]_D^{25}$ 0·56°.[5] Chromatographic analysis of the sample indicated the presence of 3·3 per cent *trans*-2-butene and 5·3 per cent *cis*-2-butene. This was sufficient alkene to account for the high density of the sample.

SUMMARY

The reductive opening of the thiirane ring with lithium aluminum deuteride has been demonstrated to proceed with inversion of configuration. This is consistent with the steric course of similar reductions of 2-bromobutane, 2-methanesulfonoxybutane, and 2,3-epoxybutane.

[21] R. Mozingo, D. E. Wolf, S. A. Harris and K. Folkers *J. Amer. Chem. Soc.* **65**, 1013 (1943).

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THE STRUCTURE OF PENDULIN AND PENDULETIN: A NEW FLAVONOL GLUCOSIDE ISOLATED FROM *BRICKELIA PENDULA*

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(*Received* 22 *March* 1957)

Abstract—The structure of a new flavone called penduletin (II), isolated as its glucoside (pendulin I) from *Brickelia pendula*, was established to be the 4′,5-dihydroxy-3,6,7-trimethoxy flavone. In pendulin, a glucose molecule is attached at the 4′ position.

WE have been interested for some time in the study of Mexican plants to which medicinal properties have been attributed. Among them are several species of plants known as *Atanasia amarga* that have a bitter taste and which are used as remedies for "stomach ailments". In a preliminary study carried out by Río de la Loza[1] it was reported that one of these *Atanasia amarga* (*Brickelia squarrosa*) contained a white glycoside, which was called "Brickelina".

We have found one of these species (which was classified as *Brickelia pendula**) in Contreras, near Mexico City.

Exhaustive extraction of the dried plant with alcohol yielded a green mass which on recrystallization from ethanol furnished a yellow crystalline substance which we have called *pendulin* (I), m.p. 178–179°; $[\alpha]_D^{20°}$ — 34° (pyridine) and empirical formula $C_{24}H_{26}O_{12}$. The infrared (Fig. 1), showed bands at 3200 (associated alcohol); 1660 (α-β unsaturated carbonyl); 1600 (aromatic ring); 1300–1180 [complex structure (multiple bands of medium intensity) due to absorption by the carbonyl and the methoxyls]; 1090 (alcoholic OH) and 838, 794 and 810 cm^{-1} (polysubstituted aromatic rings, which correspond to hydroxyl, methoxyl, ketone and phenyl groupings). λ_{max} 212, 272, 332 mμ; ε, 38,166; 23,013; 22,040.

Paper chromatography of this substance showed only one spot supporting the view that it is a pure substance.

From its empirical formula, physical constants and the different colors which it produced with specific reagents we came to the conclusion that the substance has a flavonoid structure monosubstituted with a carbohydrate.

It is difficult to hydrolyze pendulin but by prolonged boiling with strong acid a new substance was obtained which we have called penduletin (II). Its empirical formula is $C_{18}H_{16}O_7$; m.p. 216–217°. The infrared (Fig. 2) showed bands at 3100 (alcohol); 1660 (carbonyl); 1300–1180 (methoxyls) and 762 cm^{-1} (new band); λ_{max} 212, 271, 341 mμ; ε, 33,376; 19,231; 22,767. The substance has three methoxyl groups and forms a diacetate $C_{22}H_{20}O_9$ which on saponification regenerates penduletin (II). By methylation a pentamethoxy substance ($C_{20}H_{20}O_7$) (III) is obtained, while on ethylation a new compound ($C_{20}H_{20}O_7$) (IV) is formed corresponding to a monohydroxy-, mono-ethoxy-, trimethoxy-flavonoid. The sugar moiety was identified by paper chromatography and by its osazone as glucose. From the analysis before and

* We wish to thank Dr. F. Miranda of the Instituto de Biología of the Universidad Nacional Autónoma de México for his help in finding this plant and botanically classifying it.

[1] F. Río de la Loza *Materia Médica Mexicana*. Part I, p. 269 (1894).

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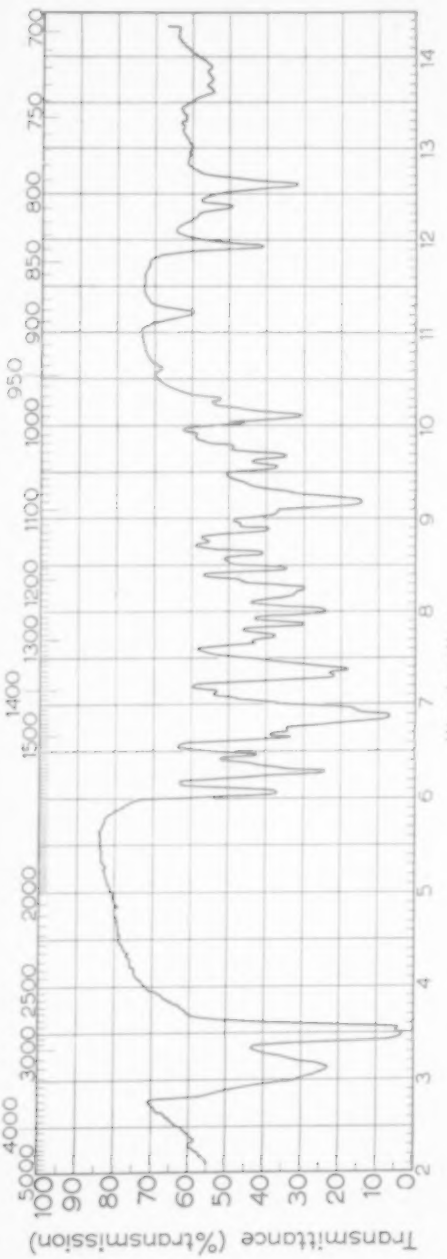


FIG. 1. Pendulin (I).

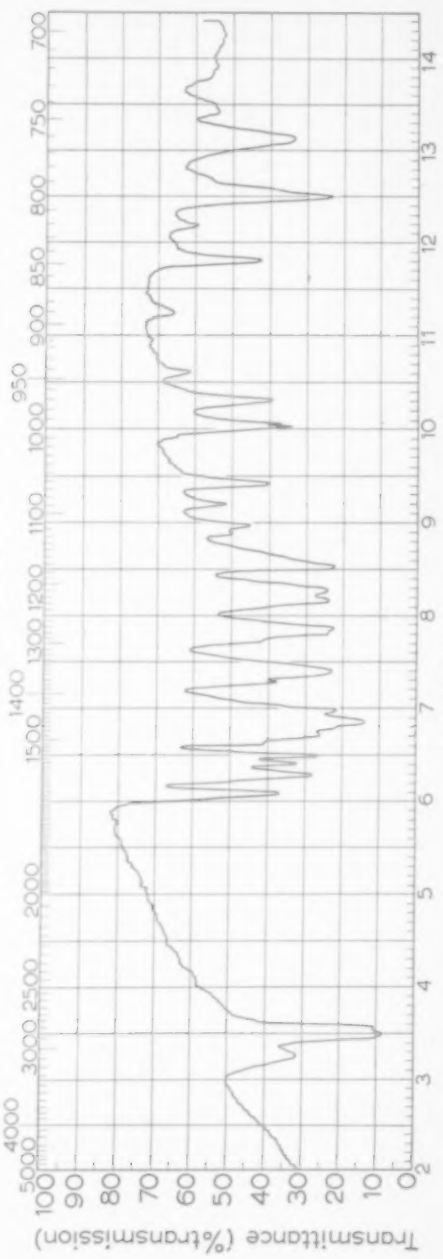


FIG. 2. Penduletin (II).

after hydrolysis it follows that pendulin is a trimethoxy-dihydroxy-flavonol or flavone substituted with one molecule of glucose.

By demethylation of compounds (II), (III) and (IV) a pentahydroxy compound (V) $C_{15}H_{10}O_7$ is obtained which by methylation regenerates the pentamethoxy flavone (III), demonstrating that demethylation does not produce rearrangement.[2] To prove that acid hydrolysis of pendulin does not produce rearrangement, it was methylated, hydrolyzed and remethylated, and gave (III).

When (III) was fused with potassium hydroxide it was completely destroyed, but by fission in alkaline solution it was possible to isolate *p*-methoxybenzoic acid. By ozonolysis of (III) we obtained the same acid exclusively. These facts demonstrate that the phenyl ring *B* of penduletin contains only one substituent, hydroxyl or methoxyl, present at the 4′position.

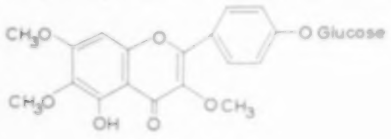
Compound (V) gives a series of color reactions identical to those reported by Goldsworthy and Robinson[3] for a synthetic 3,4′,5,6,7-pentahydroxy-flavonol, the pentamethyl ether of which was supposed to be identical with tangeretin isolated by Nelson.[4] Recently Robinson has published a note[5] in which he proves that this synthetic compound is different from tangeretin. A sample of the pentamethyl ether of the synthetic compound of Goldsworthy and Robinson* showed the same infrared spectrum as our compound (III) and did not depress its melting point.

From this comparison, it follows that the five methoxyl groups of (III) are at positions 3,4′,5,6 and 7. In penduletin three of the substituents occur as methoxyls and two as free hydroxyls.

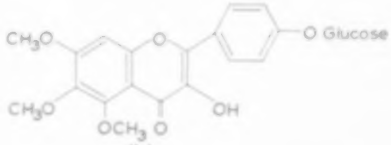
To determine the position of the glucosidic linkage pendulin (I) was methylated with diazomethane giving a tetramethoxy compound $C_{25}H_{28}O_{12}$ (VI) slightly more water soluble and with a bitter taste. By acid hydrolysis of (VI) we obtained a monohydroxy-tetramethoxy compound (VII) $C_{19}H_{18}O_7$.

By acetylation of (VII) the monoacetate (VIII) was obtained, which on ozonolysis gave *p*-acetoxybenzoic acid proving that the glucose in pendulin (I) is attached to the hydroxyl in position 4′.

There are, therefore, only two possible structures for pendulin: it must be either the 4′-glucoside of 4′,5-dihydroxy-3,6,7-trimethoxyflavone (I) or the 4′-glucoside of 3,4′dihydroxy-5,6,7-trimethoxyflavone (Ia).



(I)



(Ia)

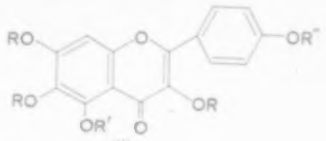
A decision in favor of (I) can be reached on the following grounds: (a) Ethylation of penduletin (II) with excess diethylsulfate and alkali introduces only *one* ethyl group, forming the 4′-ethyl derivative (IV). It is well known that ethylation of a 3-hydroxyl group proceeds readily under these conditions (cf. the ethylation of quercetin and morin[6]). On the other hand, survival of a 5-hydroxyl group under similar conditions

* We wish to thank Sir Robert Robinson for supplying us with this compound.

[2] S. K. Mukerjee and T. R. Seshadri *Chem. & Ind. (Rev.)* 271 (1955).
[3] L. J. Goldsworthy and R. Robinson *J. Chem. Soc.* 46 (1937).
[4] E. K. Nelson *J. Amer. Chem. Soc.* **56**, 1392 (1934).
[5] L. J. Goldsworthy and R. Robinson *Chem. & Ind. (Rev.)* 47 (1957).

is well documented.[6] (b) Treatment of the 4′-ethylether (IV) with acetic anhydride and sodium acetate in the cold produced no acetylation of the remaining free hydroxyl group. The 3-hydroxyl group of e.g. quercetin is easily acetylated under these conditions while the 5-hydroxyl is not touched.[7] (c) Finally, it is in keeping with the presence of the 5-hydroxylflavone system that the boric acid color test described by Wilson is positive, whereas a 3-hydroxyflavone without a 5-hydroxyl group, such as fisetin, gives a negative test.[8]

We conclude that pendulin and penduletin are correctly represented by (I) and (II), respectively.



(II)

(II) $R = CH_3$; $R' = R'' = H$

(III) $R = R' = R'' = CH_3$

(IV) $R = CH_3$; $R' = H$; $R'' = CH_3—CH_2—$

(V) $R = R' = R'' = H$

(VI) $R = R' = CH_3$; R'' = glucose

(VII) $R = R' = CH_3$; $R'' = H$

(VIII) $R = R' = CH_3$; $R'' = OAc$

EXPERIMENTAL*

Isolation of pendulin (I)

The sun dried plant (2·8 kg) was finely ground in a mikro-pulverizer mill and was extracted with three 10 l. portions of boiling alcohol. The combined extracts were concentrated under vacuum to a volume of 3 l. giving a very viscous green mass which was washed 5 times with 2 l. of hot hexane. The residue was a yellow powder, which was dissolved in alcohol, decolorized with Norite, recrystallized several times from alcohol and then from acetone–hexane from which 30 g of the glucoside *pendulin* (I) was obtained with m.p. 178–179°; $[\alpha]_D^{22} - 34°$ (pyridine), λ_{max} 212, 272, 332 mμ; ε, 38,166; 23,013; 22,040.

Anal. Calcd. for $C_{21}H_{20}O_{12}$: C, 56·91; H, 5·17; O, 37·91. Found: 57·13; H, 5·28; O, 37·72.

Calcd. for 3 methoxyls: 18·4. Found: 17·97.

* The microanalyses were carried out by Dr. Franz Pascher, Bonn, Germany. Absorptions in the ultraviolet were measured in ethanolic solution in a Beckman DK2 instrument. Infrared determinations were carried out on the Perkin-Elmer double beam model 21C spectrophotometer and were done in Nujol. Melting points are uncorrected and were determined in a Kofler block.

[6] A. G. Perkin and S. Phipps *J. Chem. Soc.* **85,** 56 (1904); J. Herzig *Mh. chem.* **5,** 72 (1884); **9,** 537 (1888); A. S. Gomm and M. Nierenstein *J. Amer. Chem. Soc.* **53,** 4408 (1931); A. G. Perkin *J. Chem. Soc.* **103,** 209 (1913).

[7] O. Kubota and A. G. Perkin *J. Chem. Soc.* **127,** 1889 (1925).

[8] C. W. Wilson *J. Amer. Chem. Soc.* **61,** 2303 (1939).

[9] T. B. Gage, C. D. Douglas and S. H. Wender *Analyt. Chem.* **23,** 1582 (1951).

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In order to test the purity of the glucoside a paper chromatogram was carried out on Whatman No. 1 filter paper using *n*-butyl alcohol–acetic acid–water 40/10/50 at 23° and developing over 8 hr. The dried paper was observed in ultraviolet and visible light. This showed only one spot with $R_f = 0{\cdot}76$.[9*]

Hydrolysis of the glucoside (I)

(I) After attempts to hydrolyze (I) with 5 per cent hydrochloric acid the glucoside was recovered unchanged. It was then hydrolyzed by dissolving 0·5 g in 300 ml of aqueous alcohol (70 per cent) containing 15 per cent of HCl. The mixture was boiled for 6 hr and was then diluted with 1 l. of water and extracted 4 times with 200 ml of ethyl acetate. The combined extracts were dried with sodium sulfate and evaporated to dryness. The residue was crystallized from alcohol–water and then from acetone–water thus producing 0·3 g of pale yellow *penduletin* (II) m.p. 216–217°; λ_{max} 212, 271, 341 mμ; ε, 33,376; 19,231; 22,767.

Anal. Calcd. for $C_{18}H_{16}O_7$: C, 62·79; H, 4·68; O, 32·53. Found: 62·98; H, 4·76; O, 32·53.

Calcd. for 3 methoxyls: 27·03. Found: 26·05.

Identification of the carbohydrate

The aqueous fraction from the acid hydrolysis was concentrated under vacuum to a volume of 500 ml. After neutralization, the liquid gave positive reactions with Fehling and Tollens reagents.

A parallel paper chromatogram was carried out with a small fraction of the aqueous extract and with a solution of glucose, developing according to the Horrocks and Manning technique.[11] The two spots thus obtained were identical.

Microscopic observation of the osazone[12] and its melting point showed that it was glucosazone. A parallel paper chromatogram of this product and of an authentic sample of glucosazone, following a technique similar to that reported by Burton, Zaffaroni and Keutmann[13] and used by Muñoz,[14†] confirmed it.

Color reactions of penduletin (II)

By treating the alcoholic solution of penduletin with sodium amalgam a crimson coloration was obtained. On treating the original solution with hydrochloric acid and magnesium a pink color was obtained.[15] Penduletin in concentrated sulfuric acid solution gave an intense yellow color. The color reactions point to a flavonol.[16]

Acetylation of penduletin (II)

Penduletin (0·5 g) was dissolved in acetic anhydride (60 ml), 2 drops of perchloric acid were added and the solution allowed to remain at room temperature for 40 min. It was then diluted with 500 ml of water and kept for 6 hr. The solution was then

* We wish to thank Dr. Barbarin Arreguin of this Institute for carrying out this experiment.

† E. Muñoz used, in the separation of osazones, Whatman No. 1 filter paper previously washed with water and ethanol, using as mobile phase chloroform saturated with formamide and as stationary phase formamide-methanol in equal parts, by volume.

[11] R. H. Horrocks and G. B. Manning *Lancet* **256**, 1042 (1949).
[12] W. Z. Hassid and R. M. McCready *Industr. Engng. Chem. (Anal.)* **14**, 683 (1942).
[13] R. B. Burton, A. Zaffaroni and E. H. Keutmann *J. Biol. Chem.* **188**, 763 (1951).
[14] E. Muñoz, Thesis Separación identificación y determinación cuantitativa de algunas osazonas por cromatografía en papel. Instituto Politécnico Nacional, México (1955).
[15] W. K. Warburton *Quart. Reviews* **VIII**, 70 (1954).
[16] T. A. Geissman *Moderne Methoden der Planzenanalyse* (Edited by K. Paech and M. V. Tracey) Vol. III, p. 470 (1955).

extracted with 3 × 50 ml portions of ethyl acetate. The organic layer was washed with cold 3 per cent aqueous sodium hydroxide and then with distilled water until neutral and was then evaporated to dryness. The residue was crystallized from acetone–hexane and gave 0·4 g of the acetylated product, m.p. 157–158°.

Anal. Calcd. for $C_{22}H_{20}O_9$: C, 61·68; H, 4·71; O, 33·61. Found: C, 62·00; H, 4·88; O, 33·27.

Calcd. for 2 acetyls: 20·00 Found: 21·96.

Saponification of diacetyl penduletin

The diacetate (0·1 g) was saponified by boiling it for 1 hr with alcoholic sodium hydroxide. The solution was processed as usual. The product (0·07 g) had m.p. 216–217° and the mixed m.p. with (II) gave no depression. The infrared spectra were also identical.

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Methylation of penduletin (II)

Penduletin (0·5 g) was methylated with diazomethane using the usual technique. A white product (III) (0·35 g) was obtained, which after crystallization from ethanol and then from acetone–hexane showed m.p. 152–153°.

Anal. Calcd. for $C_{20}H_{20}O_7$: C, 64·51; H, 5·41; O, 30·08. Found: C, 64·80; H, 5·22; O, 30·07.

Calcd. for 5 methoxyls: 41·60 per cent. Found: 40·88 per cent.

Monoethylation of penduletin (II)

Penduletin (0·5 g) was dissolved in 100 ml of ethanol to which 20 ml of 20 per cent sodium hydroxide in 70 per cent aqueous ethanol solution was added. Then 10 ml of diethyl sulfate was slowly added, the mixture was boiled for 30 min and an additional 20 ml of diethyl sulfate was added. The solution was boiled for another 5 hr, keeping it alkaline all the time. After cooling it was diluted with 300 ml of water and extracted with ethyl acetate. Evaporation of the solvent and crystallization of the residue from ethanol–water and from acetone–hexane gave 0·31 g of compound (IV), with m.p. 166–167°; λ_{max} 212, 272, 336 mμ; ε, 39,690; 22,138; 24,711.

Anal. Calcd. for $C_{20}H_{20}O_7$: C, 64·51; H, 5·41; O, 30·08. Found: C, 64·79; H, 5·44; O, 29·99.

Calcd. for 4 methoxyls (one ethoxyl as methoxyl) 33·33. Found: 32·22.

Calcd. indirectly for 3 methoxyls: 25·00. 1 ethoxyl: 12·10. Found: 24·14. 11·73.

The acetylation of IV was done as in the case of penduletin (II) and the acetate had m.p. 149–150°.

Demethylation of penduletin (II)

Demethylation in the usual manner with 47 per cent hydriodic acid and acetic anhydride, gave a product that still contained one methoxyl m.p. 286–289° (d).

Anal. Calcd. for $C_{16}H_{12}O_7$: C, 60·76; H, 3·82. Found: 60·94; H, 4·01.

Calcd. for one methoxyl: 9·80. Found: 9·07.

Demethylation under more energetic conditions leads to the pentahydroxy flavonol. To a solution of 0·4 g of penduletin (II) in 10 ml of propionic anhydride, 0·3 g of phenol and 18 ml of freshly distilled 55 per cent hydriodic acid were added. The mixture was boiled for 2 hr and was then diluted with 100 ml of water. It was

extracted with ether and with ethyl acetate. The bulked organic fractions were washed three times with an aqueous solution of sodium thiosulfate to eliminate the iodine liberated during the reaction. After drying and evaporating the solvents the residue was crystallized twice from acetone–hexane from which 0·15 g of (V) was obtained. The melting point is not definite and the substance begins to decompose at 290° and chars between 314 and 320°.

Anal. Calcd. for $C_{15}H_{10}O_7$: C, 59·61: H, 3·34; O, 37·06. Found: C, 59·01; H, 3·59; O, 37·20.

By acetylation of (V) the penta-acetate is obtained, m.p. 234–235°.

By methylation with diazomethane by the usual technique (V) regenerates (III) proving that no rearrangement occurred during the demethylation.

Alkaline fission

Half a gram of (III) was dissolved in 50 ml of ethanol and 50 ml of 20 per cent potassium hydroxide in water–alcohol was added. The mixture was boiled for 20 hr, then concentrated, diluted with water and saturated with carbon dioxide. By extraction with ether no phenolic fraction was obtained. The aqueous solution was acidified with hydrochloric acid and extracted with ether. The ethereal fractions were evaporated under vacuum and the residue was recrystallized from acetone–water when 0·05 g of an acid with m.p. 183–184° was obtained. The mixed melting point with an authentic sample of *p*-methoxy-benzoic acid was not depressed and the infrared spectra were identical. A similar fission with (IV), gave an acid which showed m.p. 194–195°. The m.p. was not depressed when mixed with an authentic sample of *p*-ethoxybenzoic acid and the infrared spectra were the same.

Ozonolysis of penduletin (II)

A solution of 0·1 g of the diacetate of penduletin in 40 ml of anhydrous ethyl acetate was ozonized for 7 min in a T23 Welsbach ozonator with 0·02 flow of oxygen at a pressure of 8 lb and 90 V. The ozonide was decomposed by catalytic hydrogenation using 5 per cent palladium on charcoal. The amount of hydrogen absorbed was 150 ml. The catalyst was filtered and the residue after removal of the solvent was crystallized from acetone–benzene and sublimed under high vacuum (0·01 mm and 125°). An acid (0·02 g) was obtained of m.p. 188–190°; the mixed melting point with *p*-acetoxybenzoic acid was not depressed and the infrared spectra were identical.

This method gives much better yields than the alkaline fission and might be used advantageously in similar cases.

Color reactions of the pentahydroxy flavonol (V)

With hydrochloric acid and magnesium a pink color was obtained; with lead acetate in alcoholic solution an orange precipitate was formed that later turned brown. With ferric chloride a dark olive green was obtained. These reactions were exactly like those reported by Robinson[3] for 3,4′,5,6,7,-pentahydroxy-flavonol.

The position of the 5 hydroxyls was proved by comparison of the dimethoxy-penduletin (III) with 3,4′,5,6,7-pentamethoxy-flavone kindly supplied by Sir Robert Robinson. The mixed melting point was not depressed and the infrared spectra were exactly alike.

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Methylation of pendulin (I)

It is difficult to methylate the glucoside with diazomethane under normal conditions. In order to methylate it an ethereal solution of diazomethane, obtained from 18 g of nitrosomethyl urea, was added to 1 g of pendulin dissolved in methanol and the solution was allowed to stand for 24 hr. At that time a fresh solution of diazomethane, obtained from 10 g of nitrosomethyl urea was added, and this treatment was repeated after 24 hours. At the end of the third 24 hr period the solution was evaporated under vacuum without applying heat. The dry residue was dissolved in anhydrous acetone and chromatographed on "Magnesol" (150 g). The column was eluted first with acetone, then with ethyl acetate saturated with water and then with 50 per cent aqueous ethanol.[17] The desired product was obtained from this last solvent after evaporation to dryness, crystallization from alcohol–water and from acetone–water, all in a nitrogen atmosphere. A water soluble compound (VI) (0·6 g) was obtained which had a bitter taste and melted at 227–228° (d) λ_{max} 212, 267, 326 mμ; ε, 39, 651; 27, 627; 29, 695.

Anal. Calcd. for $C_{25}H_{28}O_{12}$: C, 57·69; H, 5·42; O, 36·89. Found: 57·58; H, 5·63; O, 36·94.

Calcd. for 4 methoxyls: 23·85. Found: 23·82.

Hydrolysis of methoxy pendulin (VI)

A solution of 0·8 g of (VI) in 50 ml of a 10 per cent aqueous ethanolic solution of hydrochloric acid was boiled for 3·5 hr. It was diluted with 100 ml of water and extracted 3 times with 40 ml of ethyl acetate. After the usual work-up the product was crystallized from ethanol–water giving 0·4 g of (VII) m.p. 253–254°. λ_{max} 212, 260, 330 mμ; ε, 38,871; 19,630; 26,641.

Anal. Calcd. for $C_{19}H_{18}O_7$: C, 63·68; H, 5·06; O, 31·25. Found: 64·06; H, 4·84; O, 31·21

Calcd. for 4 methoxyls: 34·63. Found: 34·64.

Methylation of (VII)

Compound (VII) (0·2 g) was methylated by the usual technique with diazomethane giving 0·12 g of a compound which proved to be the same as (III) by mixed melting point and infrared spectra.

By acetylation of (VII) (0·15 g) carried out as before a mono-acetate (VIII) was obtained (0·08 g) m.p. 151–153° (d).

Ozonolysis of the acetate (VIII)

The monoacetate (VIII) (0·075 g) was dissolved in anhydrous ethyl acetate and ozonized, as in the previous case, for 3 min. The ozonide was hydrogenated with 0·1 g of 5 per cent palladium on charcoal. It absorbed 100 ml of hydrogen. The catalyst was filtered off and the solvent evaporated. The residue was crystallized from acetone–benzene and sublimed under high vacuum (0·01 mm and 125°). A product (0·013 g) was obtained which melted at 188–190° and the m.p. was undepressed when the substance was mixed with an authentic sample of *p*-acetoxybenzoic acid. The infrared spectra of the samples were identical. It is therefore concluded that the glucose molecule is attached to the 4′ position of penduletin (II).

[17] C. H. Ice and S. H. Wender *Analyt. Chem.* **24**, 1616 (1952).

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NEIGHBORING HYDROGEN, ISOTOPE EFFECT, AND CONFORMATION IN SOLVOLYSIS OF 3-METHYL-2-BUTYL *p*-TOLUENESULFONATE*[1]

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Abstract—In connection with hydrogen participation in solvolysis, 3-methyl-2-butyl *p*-toluenesulfonate is a marginal system. Comparison of the behavior of 3-D-3-methyl-2-butyl toluenesulfonate with that of the undeuterated analog discloses a substantial isotope effect on solvolysis rate, but only a small effect on product composition. The evidence points to a relatively high value of (k_Δ/k_s), the ratio of rate constants for anchimerically assisted and unassisted solvolysis processes. Conformational considerations make understandable the relatively low degree of rate acceleration displayed by 3-methyl-2-butyl toluenesulfonate.

IN connection with hydrogen participation in solvolysis, 3-methyl-2-butyl *p*-toluenesulfonate (I) is a marginal system.[2] Thus, as summarized in Table 1, acetolysis rates of the secondary alkyl *p*-bromobenzenesulfonates, $RCH(OBs)CH_3$, pass through a shallow maximum at R=*i*-Pr as R is varied from Me to *t*-Bu.[2] However, it is not easy to conclude that acetolysis of *i*-$PrCH(OBs)CH_3$ is accelerated by *tert.*-hydrogen participation, since β-Me substitution not only favors hydrogen participation, but causes several other effects[2]. For anchimerically[3] unassisted solvolysis, the sequence of rates for the various R groups, Me < Et < *i*-Pr < *t*-Bu, is predicted[2] on the basis of (i) polar and (ii) steric accelerative effects of R. The opposite order is predicted[2] from consideration of (iii) hyperconjugative and (iv) steric retarding effects of R.

The same set of effects, (i)–(iv), is associated also with change of R in the series,[4] $RCCl(CH_3)_2$, and yet the net effect of β-methyl substitution on rate of ionization in the *tertiary* series is close to zero (Table 1). Therefore, the reactivity pattern in solvolysis of $RCH(OBs)CH_3$ was taken previously as a suggestion that solvolysis rate of *i*-$PrCH(OBs)CH_3$ was influenced by a driving force due to hydrogen participation.[2c] The relatively high reactivity of the *i*-$PrCH(OBs)CH_3$ member of its series is actually obscured by the rough single-term $\rho^*\sigma^*$ correlation of solvolysis rates recently reported by Streitwieser.[5] This correlation, which takes account only of the polar effect (i) above with the aid of Taft's polar substituent constants,[6] predicts an anchimerically unassisted rate constant k_s nearly as large as the observed rate

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[1] S. Winstein *Fifteenth National Organic Chemistry Symposium of the American Chemical Society, Rochester, N.Y.* p. 29 of Abstract (1957).

[2] (a) S. Winstein *Bull. Soc. Chim. Fr.* **18**, 55 (1951); (b) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber and J. Corse *J. Amer. Chem. Soc.* **74**, 1113 (1952); (c) S. Winstein and H. Marshall *Ibid.* **74**, 1120 (1952).

[3] S. Winstein, C. R. Lindegren, H. Marshall and L. L. Ingraham *Ibid.* **75**, 147 (1953).

[4] H. C. Brown and R. S. Fletcher *J. Amer. Chem. Soc.* **71**, 1845.

[5] A. Streitwieser, Jr. *Ibid.* **78**, 4935 (1956).

[6] R. W. Taft, Jr. *Ibid.* **75**, 4231 (1953).

constant for acetolysis of *i*-PrCH(OBs)CH_3 (Table 1). However, the single-term $\rho^*\sigma^*$ correlation fails rather badly to account for the rate sequence in the *tertiary* series, $RCCl(CH_3)_2$ (Table 1).

TABLE 1. SUMMARY OF STRUCTURAL RATE SEQUENCES IN SOLVOLYSIS

	Relative Rates			
	$RCH(OBs)CH_3$ AcOH, 25°		$RCCl(CH_3)_2$ 80% EtOH, 25°	
R	Obs.[a]	Calc.[a]	Obs.[b]	Calc.[b]
Me	1·0	1·0	1·00	1·0
Et	2·3	2·2	1·65	2·1
i-Pr	6·0	5·0	0·95	4·6
t-Bu	2·9	13·1	1·21	11·5

[a] $\log k/k^0 = -3{\cdot}49\sigma^*$; Ref. 5
[b] $\log k/k^0 = -3{\cdot}3\sigma^*$; Ref. 5

As indicated previously,[2c] comparison of the behavior of 3-D-3-methyl-2-butyl *p*-toluenesulfonate with that of the undeuterated analog is helpful here, and we can now outline the results of this study.

TABLE 2. SUMMARY OF k^H/k^D FACTORS IN SOLVOLYSIS OF 3-DEUTERO-3-METHYL 2-BUTYL[a] *p*-TOLUENESULFONATE

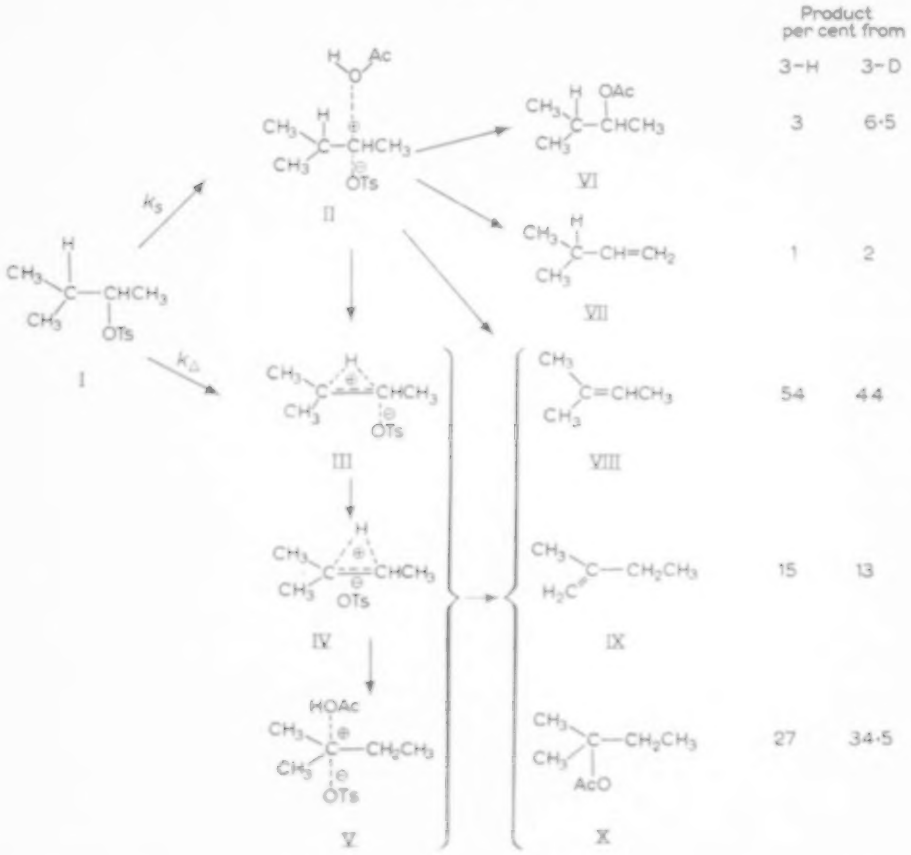
Temp. °C	80% EtOH	AcOH	HCOOH
75°	1·85 ± 0·04	1·93 ± 0·10	
50°		2·06 ± 0·08	
25°	2·05[b]	2·15[b]	2·13 ± 0·10
25° (corr.)[c]	2·14[b]	2·26[b]	2·24

[a] A deuterium analysis of 0·94 deuterium atom per molecule of the 3-D-3-methyl-2-butanol was kindly determined through the courtesy of Dr. N. R. Trenner of Merck and Co., Rahway, N.J.
[b] Extrapolated from the data at the other temperatures.
[c] Corrected approximately for deuterium content of the deuterated toluenesulfonate during main portion of rate runs.

The 3-D-3-methyl-2-butanol was prepared from the Grignard reagent from 2-D-2-propyl bromide and acetaldehyde. The isotope factors obtained from comparison of first order solvolysis rate constants of 3-D-3-methyl-2-butyl *p*-toluenesulfonate and its undeuterated analog I are sizable, being 2·25 in acetic and formic acid solvents (Table 2). As summarized in Table 3, essentially the whole of the product from solvolysis of 3-methyl-2-butyl *p*-toluenesulfonate (I) in acetic acid at 75° in the presence of a slight excess of sodium acetate involves either loss or migration of the *tertiary* hydrogen atom. Only 1 per cent of 3-methyl-1-butene (VII) and 3 per cent of unrearranged acetate VI were observed. From the 3-D-3-methyl-2-butyl ester, 59

per cent elimination was observed instead of 70 per cent with the undeuterated analog. Also, the percentages of 3-methyl-1-butene (VII) and unrearranged acetate VI were increased to 2 and 6·5 per cent, respectively.

TABLE 3



The small response of the observed kinetic isotope factor to solvent variation and the small isotope effect on product composition suggest that solvolytic processes involving nucleophilic attack on hydrogen or carbon are relatively unimportant in acetic acid solvent. It seems best to discuss the acetolysis of 3-methyl-2-butyl toluenesulfonate (I) in terms of two independent solvolytic processes, anchimerically unassisted solvolysis with rate constant k_s, and anchimerically assisted solvolysis with rate constant k_Δ. From intermediate II in the anchimerically unassisted solvolysis is obtained unrearranged acetate VI, 3-methyl-1-butene (VII) and 2-methyl-2-butene (VIII), together with a certain amount of rearranged olefin IX and rearranged acetate X as a result of *tertiary* hydrogen involvement with C_α in a step subsequent to the rate-determining one. Anchimerically assisted ionization through a transition state such as III leads to 2-methyl-2-butene (VIII), rearranged olefin IX and rearranged acetate X. A substantial ratio of (k_Δ/k_s) in acetolysis of 3-methyl-2-butyl toluenesulfonate

(I) is indicated by the composition of observed acetolysis products together with the size of the observed kinetic isotope factor.

The observed kinetic isotope factors are of a different order of magnitude from those for the secondary hydrogen isotope effects observed in solvolysis of systems[7–10] whose structure[2] does not favor anchimerically assisted ionization. As summarized in Table 4, the factor per β-deuterium atom varies from 1·10 to 1·28 for a *primary* to a *tertiary* deuterium atom adjacent to a *tertiary* center and is ca. 1·2 for a *secondary* deuterium atom adjacent to a *secondary* center. The factor observed for the *tertiary* deuterium atom in the 3-methyl-2-butyl system, 2·25, is of the same order as that observed in the intermolecular electrophilic substitution of triphenylcarbonium ion on 2-D-2-propanol.[11,12]

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In using the observed isotope factors, it helps to distinguish between three factors: (i) I, the overall isotope factor; (ii) I_Δ, the isotope factor for anchimerically assisted ionization, namely k_Δ^H/k_Δ^D; (iii) I_s, the isotope factor for the anchimerically unassisted solvolysis, namely k_s^H/k_s^D. I may be expressed as in equation (1), three other useful derived equations being (2), (3), and (4). Using equation (2) with an anticipated value for I_s of the order of

$$I = \frac{k^H}{k^D} = \frac{k_\Delta^H + k_s^H}{k_\Delta^D + k_s^D} = \frac{1 + (k_\Delta^H/k_s^H)}{(k_\Delta^D/k_s^H) + (k_s^D/k_s^H)} \tag{1}$$

$$I_s = \frac{k_s^H}{k_s^D} = I\left[\frac{1 + (k_\Delta^D/k_s^D)}{1 + (k_\Delta^H/k_s^H)}\right] \tag{2}$$

$$I = \frac{k^H}{k^D} = I_\Delta\left[\frac{1 + (k_\Delta^H/k_s^H)}{(k_\Delta^H/k_s^H) + (I_\Delta/I_s)}\right] \tag{3}$$

$$I_\Delta = \frac{k_\Delta^H}{k_\Delta^D} = \frac{I(k_\Delta^H/k_s^H)}{1 + (k_\Delta^H/k_s^H) - (I/I_s)} \tag{4}$$

1·3, k_Δ^H/k_s^H is estimated to be of the order of 6, if it is to be roughly twice the value of k_Δ^D/k_s^D as the product compositions tend to indicate. On this basis, the I_Δ value, relating to anchimerically assisted solvolysis, is predicted by equation (4) to be of the order of 2·6.

The intimate mechanistic details of the formation of final products from anchimerically assisted ionization are still not clear.[1,13] The formulation in Table 3 leaves open the question of the number of intermediates such as III, IV, and V which require explicit mention and what their roles are in formation of olefins VIII and IX and rearranged acetate X. Further, III, IV, and V are arbitrarily written only as intimate ion pairs. Under the same conditions as those employed in acetolysis of 3-methyl-2-butyl toluenesulfonate (I), *t*-amyl chloride, which gives rise to *t*-amyl cationic

[7] V. J. Shiner, Jr. *J. Amer. Chem. Soc.* **75**, 2925 (1953).
[8] V. J. Shiner, Jr. *Ibid.* **76**, 1603 (1954).
[9] E. S. Lewis and C. E. Boozer *Ibid.* **76**, 791 (1954).
[10] A. Streitwieser, Jr., R. H. Jagow and S. Suzuki *Ibid.* **77**, 6713 (1955).
[11] P. D. Bartlett and J. D. McCollum *Ibid.* **78**, 1441 (1956).
[12] The similarity in k_H/k_D factors may be more than coincidental, since the bonding situation of the hydrogen or deuterium atom in question may be geometrically similar in the transition states for the two reactions. See S. Winstein, T. G. Traylor and C. S. Garner *J. Amer. Chem. Soc.* **77**, 3741 (1955), for remarks on electrophilic substitution. This point was also made independently to one of us (S.W.) by Dr. E. S. Lewis of Rice Institute of Technology.
[13] S. Winstein and N. J. Holness *J. Amer. Chem. Soc.* **77**, 5562 (1955).

species of the type of V, gives rise to 2-methyl-2-butene (VIII), 2-methyl-1-butene (IX) and *t*-amyl acetate (X) in the proportions, 59 : 26 : 15, respectively. Both the proportion of elimination and the IX : X ratio are considerably higher than in acetolysis of I.

TABLE 4. ISOTOPE EFFECTS (k_H/k_D) PER DEUTERIUM ATOM IN VARIOUS SYSTEMS AT 25°

System	80% EtOH	AcOH	HCOOH	Ref
$CH_3CH_2CCl(CD_3)_2$	1·10			7
$CH_3CD_2CCl(CH_3)_2$	1·19			7
$(CH_3)_2CDCCl(CH_3)_2$	1·28			8
$CH_3CH_2CD_2CH(OTs)CD_3$	1·08	1·13	1·13	9
trans-2-D-*cyclo*pentyl OTs		1·19		10
cis-2-D-*cyclo*pentyl OTs		1·24		10
$(CH_3)_2CDCH(OTs)CH_3$	2·15	2·27	2·24	
$(C_6H_5)_2C^{\oplus} - DC(OH)(CH_3)_2$		1·84[a,b]		11

[a] In H_2O-H_2SO_4 medium.
[b] From deuterium analyses of products; a value of 2·58 obtained from rate measurements.

The indicated relatively high k_Δ/k_s and yet the low degree of rate acceleration in acetolysis displayed by 3-methyl-2-butyl toluenesulfonate (I) becomes more understandable on the basis of conformational degeneracy[13] of the solvolysis, and differing effects of β-methyl substitution on the intrinsic rate constants associated with the different conformations of toluenesulfonate I, namely IA, B, and C.

The anchimerically assisted ionization of toluenesulfonate I is conformationally homogeneous,[13] k_Δ being given by equation (5), where N_B is the mole fraction of conformation B and k_Δ^B is the rate constant for anchimerically assisted ionization for this conformation. On the other hand, anchimerically unassisted solvolysis of toluenesulfonate I is conformationally degenerate,* k_s being given by equation (6). Steric considerations suggest that B is the least populated of

$$k_\Delta = N_B k_\Delta^B \tag{5}$$

$$k_s = N_A k_s^A + N_B k_s^B + N_C k_s^C \tag{6}$$

the three conformations of I. This contributes to a low value of k_Δ. On the other hand, A is predicted to be the most populated conformation of I and yet associated with a relatively low k_s^A value by analogy with the behavior of conformationally more homogeneous *cyclo*hexyl systems.[13,14]

Solvolysis rates of *trans*-2-methyl*cyclo*hexyl[1,15] toluenesulfonate (XII) are ca. one-third of the values for the *trans*-4-*t*-butyl*cyclo*hexyl[13] analog, a β-methyl group on an *equatorial* toluenesulfonate being noticeably rate-depressing. Analogy between conformations IA and XIIA predicts that k_s^A for IA is lower than k_s^A for the 2-butyl

* As pointed out previously,[2b] β-hydrogen hyperconjugation and hydrogen participation both involve delocalization of β-bonding electrons. Where geometry is proper, as in conformation IB, hydrogen hyperconjugation and participation can merge. Equation (6) assumes that the approximation of distinct anchimerically unassisted and assisted solvolysis processes is valid even for conformation IB.

[14] S. Winstein, B. K. Morse, E. Grunwald, H. W. Jones, J. Corse, D. Trifan and H. Marshall *J. Amer. Chem. Soc.* **74**, 1127 (1952).

[15] R. Heck unpublished work.

FIG. A

system XI. With the *cis*-2-alkyl*cyclo*hexyl toluenesulfonates, such as *cis*-2-methyl-*cyclo*hexyl[1,15] XIII or neomenthyl,[1,10,16,17] the proportion of conformation B is considerably higher than for the 3-methyl-2-butyl one and thus k_Δ given by equation (5) is higher. This makes the β-methyl group more rate-enhancing in the *cyclo*hexyl than in the 2-butyl system and thus anchimeric acceleration due to participating β-hydrogen more pronounced.

[16] J. Schwartz Unpublished work.
[17] S. Winstein 1, 2- and 1, 3-Hydrogen Shift. *Symposium on Molecular Rearrangements*. Queen Mary College, Univ. of London (1954).

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MECHANISM OF THE CLAY–KINNEAR–PERREN CONDENSATION

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Abstract—Several apparently unrelated aspects of the process whereby complexes of the type $[RPCl_3]^+[Al\ Cl_4]^-$ are formed from phosphorus trichloride, aluminium chloride and an alkyl halide, are shown to be compatible in terms of a mechanism involving preliminary formation of a carbonium cation.

CLAY,[1] and independently Kinnear and Perren,[2] have prepared alkylphosphonyl dichlorides, $RPOCl_2$, by controlled hydrolysis of the complexes formed by interaction of alkyl halides with phosphorus trichloride and aluminium chloride, the latter authors demonstrating the wide application of the reaction. Evidence was provided to show that the intermediate complexes, which were isolated in specific examples of the reaction, might be formulated $[RPCl_3]^+[AlCl_4]^-$ (I), and recent work[3] on the mechanism of the hydrolysis tends to support this. Clay proposed that the formation of complex occurred by the sequence:

$$PCl_3 + RCl \rightleftharpoons RPCl_4 \qquad \text{(i)}$$

$$RPCl_4 + AlCl_3 \longrightarrow (I) \qquad \text{(ii)}$$

Kinnear and Perren suggested the alternative reactions:

$$PCl_3 + AlCl_3 \rightleftharpoons PCl_3 : AlCl_3 \qquad \text{(iii)}$$

$$PCl_3 : AlCl_3 + RCl \longrightarrow (I) \qquad \text{(iv)}$$

The originators considered a process involving intermediate formation of carbonium cation unlikely, on the grounds that if the alkyl halide and aluminium chloride are first mixed together, a lower yield of product is obtained than if the reactants are mixed in any other order.

There is little evidence however, that phosphorus trichloride will react with either alkyl halide or aluminium chloride alone, and a carbonium cation mechanism appears more likely for the following reasons:

(a) The formation exclusively of alkyl-2-phosphonyl dichloride when an *n*-alkyl is employed in the reaction, because of the greater comparative stability of the secondary cation, and related phenomena such as the behaviour of allyl chloride, can be better understood.

(b) It explains the low reactivity of poly-halogeno compounds and the complete inactivity of vinyl chloride in the reaction.

[1] J. P. Clay *J. Org. Chem.* **16**, 892 (1951).
[2] A. M. Kinnear and E. A. Perren *J. Chem. Soc.* 3437 (1952).
[3] F. W. Hoffman, T. C. Simmons and L. J. Glunz III *J. Amer. Chem. Soc.* **79**, 3570 (1957).

(c) It may be correlated with the mechanistic interpretation placed upon the first stage (v) of the Arbusov reaction:

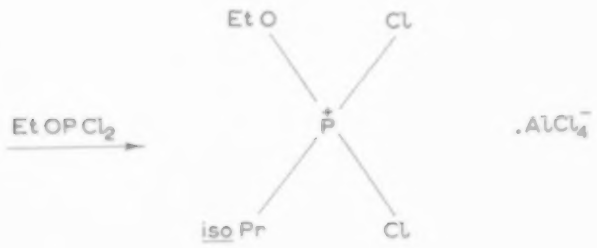
$$(RO)_3P: + R'X \longrightarrow (RO)_3PR'^{+}.X^{-} \qquad (v)$$

$$(RO)_3PR'^{+}.X^{-} \longrightarrow (RO)_2PO.R' + RX \qquad (vi)$$

In triphenyl phosphite, the nature of R is such that the first step is undoubtedly bimolecular, since the resonance stabilised phosphonium salt, which is not susceptible to the subsequent elimination (vi) can be isolated in good yield.[4] There is no real evidence that such a phosphonium salt has more than transitory existence in the reaction involving trialkyl phosphites, but Gerrard and Green[5] have shown that when triethyl phosphite and optically active (+)-1-phenylchloroethane interact, the products include diethyl 1-phenylethylphosphonate possessing a small but definite degree of activity. One may infer that the first step proceeds at least partly by an SN_2 mechanism, which accounts for this product, if predominantly by an SN_1 process. In species in which one or more RO groups are replaced by electron attracting atoms, their nucleophilic power is thereby reduced and the SN_2 character of the primary process is still further suppressed. Thus a dialkyl phosphorochloridite, $(RO)_2PCl$, will not react with an alkyl halide[5] unless some agent facilitating preliminary carbon-halogen bond fission in the latter is present, as in the subject reaction. Phosphorus trichloride evidently represents a limiting case in this respect, and it is reasonable to assume that a carbonium cation must be produced before reaction with alkyl halide will take place.

(d) The same mechanism may be invoked to account for the behaviour of an alkyl phosphorodichloridite, $ROPCl_2$, in the reaction:

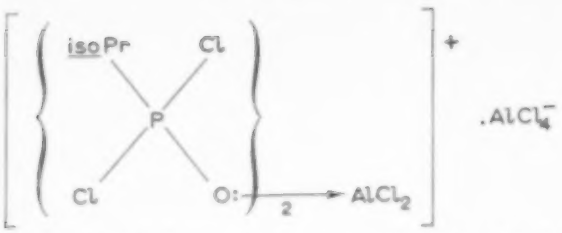
$$CH_3CH_2CH_2Cl + AlCl_3 \longrightarrow CH_3\overset{+}{C}HCH_3 . AlCl_4^-$$



(II)

In this case however, it follows that the nature of the complex, (which on hydrolysis gives *iso*propylphosphonyl dichloride), may be different from (I), and better represented:

[4] A. Michaelis and R. Kähne *Ber.* **31**, 1048 (1898).
[5] W. Gerrard and W. J. Green *J. Chem. Soc.* 2550 (1951).



It depends at what stage (II) decomposes to give ethyl chloride, a point yet to be investigated.

(e) It provides a partial explanation of the fact that a diphosphono derivative cannot be obtained from, for instance, chloromethylphosphonyl dichloride, $ClCH_2PO{\cdot}Cl_2$. Formation of the cation in this case would necessitate like charges on the adjacent carbon and phosphorus atoms, which experience shows to be a very unstable arrangement.[6] The situation is however, more complex than this as the effect would diminish rapidly down side chains of increasing length, whereas even pentamethylene dibromide gives only 5-bromopentylphosphonyl dichloride.

(f) It explains new observations on the behaviour of trimethylchlorosilane, Me_3SiCl, and chloromethyldimethylchlorosilane, $ClCH_2Si(Me)_2Cl$, in the reaction. The former takes part in the reaction very sluggishly and in its presence (1 mole), aluminium chloride (1 mole) in excess phosphorus trichloride dissolves completely only after six hours heating under reflux. Even after twenty hours, some trimethylchlorosilane can be recovered. Its carbon isologue, *tert.*-butyl chloride, gives an almost quantitative yield of complex in ten minutes. This difference in reactivity may be attributed to the difference in ease of formation between the carbonium and silonium cations in these circumstances, arising from the relative electronegativities of the carbon (2·5), silicon (1·8) chlorine (3·0) and aluminium (1·5) atoms. On the other hand, chloromethyldimethylchlorosilane (1 mole) gives after less than one hour of heating with aluminium chloride (1 mole) and excess trichloride, a complex which on alcoholysis affords a good yield of dialkyl alkoxydimethylsilylmethylphosphonate $(RO)_2PO{\cdot}CH_2Si(Me)_2OR$[7] showing that the chlorine atom attached to the carbon atom reacts preferentially.

The carbonium cation mechanism is not put forward without reservation, but formation of the complex may be provisionally considered to take place in the following manner:

$$R{-}Cl: \cdots\cdots\rightarrow AlCl_3 \xrightarrow{k_1} [RAlCl_4] \xrightarrow{k_2} R^+ + AlCl_4^- \quad \text{(vii)}$$

$$[RAlCl_4] + RCl + AlCl_3 \xrightarrow{k_3} \text{other products} \quad \text{(viii)}$$

$$Cl_3P: \cdots\cdots\rightarrow R^+ \xrightarrow{k_4} [RPCl_3]^+ \quad \text{(ix)}$$

$$[RPCl_3]^+ + [AlCl_4]^- \longrightarrow I \quad \text{(x)}$$

where $k_4 \gg k_3 < k_2$.

[6] A. E. Remick *Electronic Interpretations of Organic Chemistry*. p. 115, Wiley, New York (1949).
[7] C. W. Jefford Private communication.

Such a scheme provides for the observed effect upon yield of the order in which reactants are mixed, the "other products" in (viii) being the more intricate polynuclear complexes envisaged by Wertyporoch,[8] and recently substantiated, by Korshak and Lebedev;[9] complexes which although effective in promoting Friedel–Crafts alkylation are apparently ineffective in the subject reaction. This conclusion is compatible with a current view that Friedel–Crafts alkylation can occur by a dual mechanism, which results in formation of the mixture of *n* and *sec* substitution products obtained from an *n*-alkyl halide.

[8] E. Wertyporoch *Ber. Dtsch. Chem. Ges.* **64**, 1372 (1931).
[9] V. V. Korshak and N. N. Lebedev *Zhur. Obs. Khim. SSSR* **18**, 1766 (1948); *Chem. Abstr.* **43**, 2930 (1949).

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ANALOGUES OF MALE SEX HORMONES

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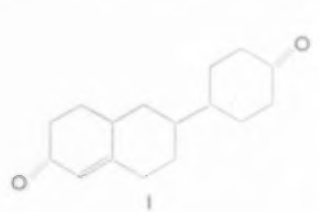
Abstract—The synthesis of *cis*- and *trans*-6-(4'-*oxo*cyclo*hexenyl*)-9-methyldecal-1-ol, which may be regarded as analogues of D-homo-testosterone, is described.

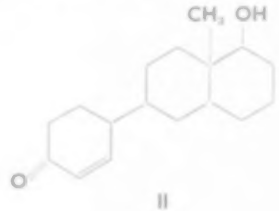
THE spectacular success of stilboestrol and hexoestrol[1] as oestrogenic hormone substitutes immediately led to an intensive search for equally simple active analogues of other sex hormones. Early approaches chiefly consisted in attaching the characteristic C_{17}-side chains of various steroidal hormones to suitable derivatives of diphenylhexane,[2] diethylstilbene,[3,4] dibenzyl[5] and even benzene;[4] a number of analogues of androgens based on perhydrohexoestrol has been described in the patent literature.[6] Some of these compounds were alleged to possess the activity aimed at,[2,4] while others were found to be totally inactive.[3]

It became gradually apparent, however, that biological activity was closely linked with the structure of the natural hormones, except in the case of the oestrogens. Although the limits within which biological activity remains unaffected by structural alterations have not yet been completely defined, they are undoubtedly very restricted;[7] and rogenic activity in particular appears to be extremely structure-specific.

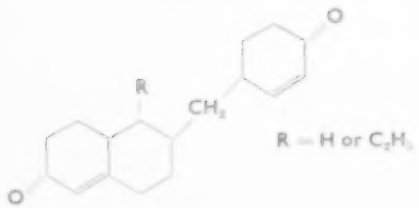
Nevertheless the hope of finding hormone substitutes amongst compounds



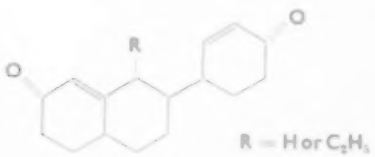
I



II



III



IV

[1] E. C. Dodds, L. Golberg, W. Lawson and R. Robinson *Proc. Roy. Soc.* B **127**, 140 (1939).
[2] The Wellcome Foundation Ltd., G. Brownlee and W. M. Duffin Brit. Pat. 550,262 (1942).
[3] R. H. Jaeger and R. Robinson *J. Chem. Soc.* 744 (1941).
[4] W. H. Linnell and I. M. Roushdi *J. Pharmacol.* **14**, 240 (1941); *Nature, Lond.* **148**, 595 (1941).
[5] W. C. J. Ross *J. Chem. Soc.* 536, 538 (1945).
[6] A. L. Wilds, C. H. Hoffman and T. H. Pearson *J. Amer. Chem. Soc.* **77**, 647 (1955).
[7] A. J. Birch and H. Smith *J. Chem. Soc.* 4909 (1956) and previous papers.

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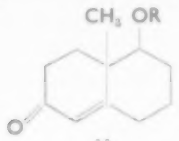
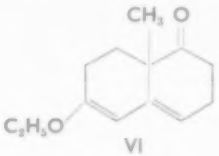
incorporating only part of the steroid molecule has not been entirely abandoned. Encouraged by the claim[8] that the diketone (I) was slightly androgenic it was at that time considered desirable to prepare an analogue of D-homo-testosterone without ring B (II). Since then several compounds bearing rather scantier likeness to the steroids than either (I) or (II)—for instance (III)[9] and (IV)[10]—have been reported as devoid of androgenic activity.

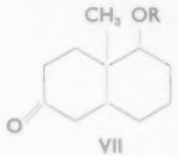
As starting material for the synthesis of the hydroxy-ketone (II) served 1-hydroxy-9-methyl-6-oxo-1:2:3:4:6:7:8:9-octahydronaphthalene (V, R = H) which was readily prepared from the enol ether (VI)[11,12] by reduction with lithium aluminium hydride and subsequent acid hydrolysis (cf.[13]). Condensation of the keto-alcohol (V, R = H) with



V



VI



VII

dihydropyran[14] gave the corresponding tetrahydropyranyl ether (V, R = $\overset{\displaystyle\diagup\!\!\diagdown}{\text{CH}}$—O—$CH_2$—$CH_2$—$CH_2$—$CH_2$) from which 9-methyl-6-oxodecal-1-ol (VII, R = $\overset{\displaystyle\diagup\!\!\diagdown}{\text{CH}}$—O—$CH_2$—$CH_2$—$CH_2$—$CH_2$) in its *cis*-form was obtained by catalytic hydrogenation, and in the *trans*-form by chemical reduction with lithium in liquid ammonia.[15] The configurations were assigned not only on the basis of the means employed for the elimination of the double bond[16] but also by hydrolysing both saturated ketones to give two hydroxy-ketones (VII, R = H) and establishing the identity of one of them (the product from catalytic hydrogenation) by comparison with a sample previously prepared by a different route for which *cis*-fusion of the rings had been rigidly proved.[17] The infra-red spectra of the two isomers (VII, R = H) differed materially in the region 8–15 μ.

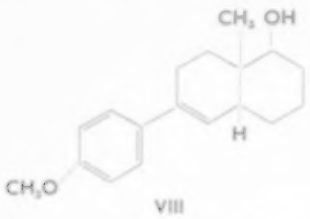
Condensation of the *cis*- and *trans*-isomers

(VII, R = $\overset{\displaystyle\diagup\!\!\diagdown}{\text{CH}}$—O—$CH_2$—$CH_2$—$CH_2$—$CH_2$)

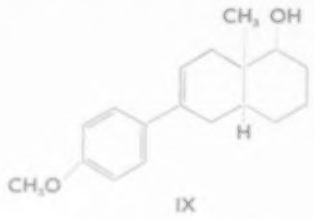
with anisyl magnesium bromide, followed by acid treatment gave the octalin derivatives (VIII) and (IX) respectively. Birch reduction with sodium—alcohol—liquid ammonia of (VIII) gave after acid hydrolysis the β:γ-unsaturated ketone (X) which could not be induced to crystallise. The infra-red spectrum with a single strong band at 5·85 μ and the absence of any appreciable light absorption in the region 200–250 mμ confirmed this structure. Reduction of the *trans*-compound (IX) with lithium and ethanol in liquid ammonia,[18] followed by carefully controlled acid hydrolysis[19] yielded the β:γ-unsaturated ketone (XI) as a gum, which on examination

[8] A. L. Wilds, C. H. Shunk and C. H. Hoffman *J. Amer. Chem. Soc.* **71**, 3266 (1949).
[9] K. W. Bentley and W. C. Firth *J. Chem. Soc.* 2403 (1955).
[10] V. S. Gaind, R. P. Gandhi and S. M. Mukherji *Chem. & Ind. (Rev.)* 1593 (1955).
[11] S. Swaminathan and M. S. Newman *Tetrahedron* **2**, 88 (1958).
[12] R. Robinson *et al.* *Tetrahedron* In press.
[13] A. J. Birch, K. A. J. Quartey and H. Smith *J. Chem. Soc.* 1768 (1952).
[14] G. F. Woods and D. N. Kramer *J. Amer. Chem. Soc.* **69**, 2246 (1947).
[15] F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi *Ibid.* **75**, 1282 (1953).
[16] E. E. van Tamelen and W. C. Proost *Ibid.* **76**, 3632 (1954).
[17] R. H. Jaeger, R. Robinson and H. Smith Unpublished work.
[18] A. L. Wilds and N. A. Nelson *J. Amer. Chem. Soc.* **75**, 5360 (1953).
[19] J. C. Sheehan and G. D. Laubach *Ibid.* **72**, 2478 (1950).

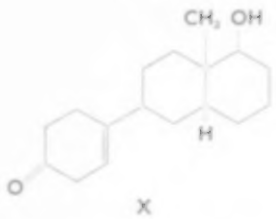
of the carbonyl region by ultra-violet and infra-red spectroscopy gave the same results as the corresponding *cis*-compound (X); furthermore, a yellow 2:4-dinitrophenylhydrazone was obtained with Brady's reagent.



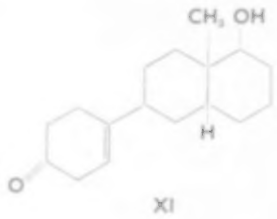
VIII



IX

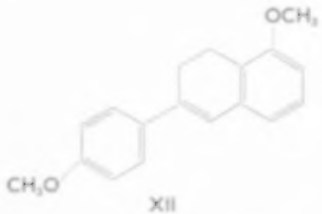


X

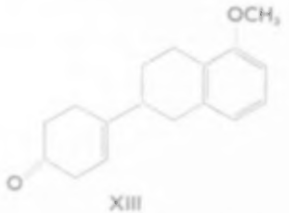


XI

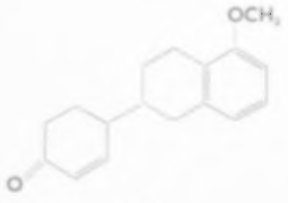
Conversion of the compounds (X) and (XI) to the isomeric α:β-unsaturated ketones (II) was only partly accomplished, treatment with sodium methoxide in methanol in each case resulting in an inseparable mixture of conjugated and unconjugated unsaturated ketones in a ratio of approximately 1:1. This estimate was supported by the light absorption at 220–225 mμ ($\varepsilon = 7000$) and by comparison of the intensity of the carbonyl bands at 5·85 and 5·99 μ. Although not entirely unexpected in view of other worker's failure to isomerise certain substituted *cyclo*hexenones,[20,21] these results were nevertheless disappointing since model experiments carried out in the early stages of this work had been completely successful in this respect.



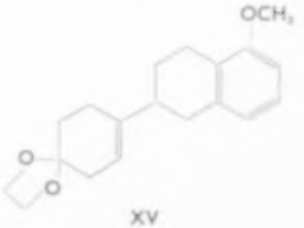
XII



XIII



XIV



XV

[20] A. J. Birch and S. M. Mukherji *J. Chem. Soc.* 2531 (1949).
[21] A. L. Wilds and N. A. Nelson *J. Amer. Chem. Soc.* **75**, 5366 (1953).

Birch reduction of the compound (XII) obtained from a reaction of 1-methoxy-6-oxo-5:6:7:8-tetrahydronaphthalene with anisyl magnesium bromide yielded after acid hydrolysis the unconjugated ketone (XIII) which gave a yellow 2:4-dinitrophenylhydrazone and did not absorb in the 200–250 mμ region. This was isomerised smoothly by means of sodium methoxide in methanol to the crystalline α:β-unsaturated ketone (XIV) with an absorption maximum at 225 mμ (ε = 15,000); with Brady's reagent a red 2:4-dinitrophenylhydrazone was formed. With the intention of reducing the remaining aromatic nucleus by the Birch–Wilds method,[18] the keto-group of (XIII) was protected by forming the cyclic ketal (XV). Other commitments, however, prevented completion of this aspect of the work.

The partially isomerised hydroxy-ketones obtained from (X) and (XI) had no androgenic activity.

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EXPERIMENTAL

Light petroleum without further specification means the fraction boiling at 60–80°. Ultra-violet light absorptions were determined in methanolic solutions; Nujol mulls were used for the infra-red spectra of solids.

6-*Ethoxy*-1:2:3:7:8:9-*hexahydro*-1-*hydroxy*-9-*methylnaphthalene*

Powdered lithium aluminium hydride (4 g) was added to a solution of 6-ethoxy-1:2:3:7:8:9-hexahydro-9-methyl-1-oxonaphthalene (VI)[11,12] (15 g) in anhydrous ether (150 cm^3). After 12 hr at room temperature the mixture was refluxed for one hour and the reaction product isolated, omitting the use of mineral acid. The crude product crystallised in contact with traces of moist ether; recrystallisation from either aqueous methanol or a concentrated ethereal solution gave fine long transparent needles, m.p. 105°. (This material liquefied in the vacuum desiccator and evidently contained solvent of crystallisation in its solid state.) (Found: C, 73·8; H, 9·4. $C_{13}H_{20}O_2 \cdot \frac{1}{4}H_2O$ requires C, 73·5; H, 9·2 per cent). The anhydrous material distilled as a yellow oil, b.p. 125–128°/0·1 mm (Found: C, 75·2; H, 9·5. $C_{13}H_{20}O_2$ requires C, 75·0; H, 9·6 per cent). Light absorption: Max. 242·5 mμ (ε = 22,000).

9-*Methyl*-1:2:3:4:6:7:8:9-*octahydro*-6-*oxo*-1-(2′-*tetrahydropyranyloxy*)-*naphthalene*

The above enol-ether (12 g), ethanol (155 cm^3), water (40 cm^3) and concentrated sulphuric acid (3·4 cm^3) were refluxed under nitrogen for 1 hr. The solution was poured into brine, the product collected in ether and washed and dried. 1-Hydroxy-9-methyl-1:2:3:4:6:7:8:9-octahydro-6-oxonaphthalene (cf.[13]) distilled as a yellow oil (7·3 g), b.p. 135–137°/0·2 mm (Found: C, 73·2; H, 9·0. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·9 per cent). Light absorption: Max. 240 mμ (ε = 14,400). The 2:4-*dinitrophenylhydrazone* crystallised from ethanol as scarlet prisms, m.p. 172° (Found: C, 56·2; H, 5·6; N, 15·3. $C_{17}H_{20}O_5N_4$ requires C, 56·7; H, 5·6; N, 15·6 per cent).

A solution of the hydroxy ketone (7·2 g) in freshly distilled dihydropyran (20 cm^3) containing a few drops of concentrated hydrochloric acid was kept at room temperature for 12 hr. After addition of ether the solution was washed with aqueous sodium carbonate and a lot of water and was dried. The crude oily product solidified on trituration with light petroleum (b.p. 40–60°) and was recrystallised from this solvent or aqueous methanol; 9-*methyl*-1:2:3:4:6:7:8:9-*octahydro*-6-*oxo*-1-(2′-*tetrahydropyranyloxy*)-*naphthalene* (5·1 g) formed colourless prisms, m.p. 62° (Found: C, 72·4;

H, 9·3. $C_{16}H_{24}O_3$ requires C, 72·7; H, 9·1 per cent). Light absorption: Max. 240 mμ ($\varepsilon = 16{\cdot}000$).

9-Methyl-6-oxo-1-(2′-tetrahydropyranyloxy)-cis-decalin

The above unsaturated ketone (5 g) dissolved in absolute ethanol (50 cm³) was hydrogenated at room temperature and ordinary pressure in the presence of 2 per cent palladised strontium carbonate (0·5 g). The product was isolated in the usual manner and distilled as a colourless oil (5 g), b.p. 135°/0·05 mm (Found: C, 71·9; H, 9·8. $C_{16}H_{26}O_3$ requires C, 72·2; H, 9·8 per cent). A small sample of this material was converted by acid hydrolysis into 9-methyl-6-oxo-*cis*-decal-1-ol, m.p. 91° which had been previously prepared and for which the *cis*-configuration had been established.[17]

9-Methyl-6-oxo-1-(2′-tetrahydropyranyloxy)-trans-decalin

To a solution of lithium (0·1 g) in liquid ammonia (110 cm³) was added dropwise one of 9-methyl-1:2:3:4:6:7:8:9-octahydro-6-oxo-(2′-tetrahydropyranyloxy)-naphthalene (1·16 g) in tetrahydrofuran (40 cm³). Ten minutes after completed addition the blue solution was decomposed with a few crystals of ammonium chloride followed by water and ether. From the ethereal extract a golden yellow oil (1·04 g) was obtained which was absorbed from light petroleum on activated alumina (30 g). Elution with mixtures of benzene—light petroleum and finally benzene alone yielded crystalline *9-methyl-6-oxo-1-(2′-tetrahydropyranyloxy)-trans-decalin* (0·90 g) which was recrystallised from very little light petroleum (b.p. 40–60°) to give colourless prisms, m.p. 98–99° (Found: C, 71·9; H, 9·9. $C_{16}H_{26}O_3$ requires C, 72·2; H, 9·8 per cent).

9-Methyl-6-oxo-trans-decal-1-ol

The above tetrahydropyranyl ether (110 mg) was refluxed under nitrogen for 30 min with methanol (5 cm³) and a few drops of dilute hydrochloric acid. The reaction mixture was poured into brine, the product extracted with ether and the extract washed and dried. The crude material solidified on trituration with light petroleum and, after chromatography on a short column of activated alumina, *9-methyl-6-oxo-trans-decal-1-ol* crystallised from light petroleum (b.p. 40–60°) as colourless prisms, m.p. 69° (Found: C, 72·8; H, 10·1. $C_{11}H_{18}O_2$ requires C, 72·5; H, 9·9 per cent). The *2:4-dinitrophenylhydrazone*, prepared with Brady's reagent, crystallised from ethanol in orange yellow prisms, m.p. 159° (Found: C, 56·5; H, 6·3; N, 15·7. $C_{17}H_{22}O_5N_4$ requires C, 56·4; H, 6·1; N, 15·5 per cent).

6-Anisyl-6-hydroxy-9-methyl-1-(2′-tetrahydropyranyloxy)-cis-decalin

A solution of 9-methyl-6-oxo-1-(2′-tetrahydropyranyloxy)-*cis*-decalin (0·75 g) in anhydrous ether (15 cm³) was added slowly in an atmosphere of nitrogen to ice-cold, well-stirred anisyl magnesium bromide (prepared from 320 mg of magnesium and 1·75 cm³ of 4-bromoanisole in 25 cm³ of ether). The mixture was kept at 0° for 30 min, then refluxed for 2 hr and finally stood at room temperature for 4 hr; decomposition at 0° with 10 per cent sulphuric acid, washing and drying of the ether layer isolated an oil, which on fractionation gave a fore-run from which 4:4′-dianisol, m.p. 174° was isolated, and as the main fraction the *carbinol* (0·8 g), pale yellow

glass, b.p. 205–210°/0·03 mm (Found: C, 73·5; H, 8·8; OMe, 8·2. $C_{23}H_{34}O_4$ requires C, 73·8; H, 9·1; OMe, 8·3 per cent).

6-*Anisyl*-1-*hydroxy*-9-*methyl*-1:2:3:4:7:8:9-cis-*octahydronaphthalene* (VIII)

The foregoing carbinol (0·55 g) was refluxed for one hour with ethanol (25 cm³) and three drops of concentrated hydrochloric acid; the mixture was then poured into water and the product isolated by means of ether. After evaporation of the solvent the residue crystallised from light petroleum as colourless, blunt needles, m.p. 147° (0·4 g) (Found: C, 79·7; H, 8·7. $C_{18}H_{24}O_2$ requires C, 79·5; H, 8·8 per cent).

Reduction. Sodium (5·75 g) in small slices was added rapidly with stirring to a solution of the above ether (600 mg) in tetrahydrofuran (15 cm³), ethanol (30 cm³) and liquid ammonia (300 cm³). After disappearance of the blue colour, water (200 cm³) was added, followed by ether (200 cm³); the organic layer was washed and the solvent evaporated. The residue (600 mg) was stirred and boiled for 20 min with 3 per cent sulphuric acid under nitrogen. The washed and dried ether extract from this yielded a thick yellow oil (0·53 g) which was absorbed on neutral alumina (15 g) in light petroleum; benzene and benzene-ether (9:1) eluted 6-(4′-*oxo*cyclo*hexenyl*)-9-*methyl*-cis-*decal*-1-*ol* which failed to crystallise and was evaporatively distilled as an almost colourless oil (400 mg), bath temperature 195° at 0·08 mm. The infra-red spectrum had strong bands at 2·95 and 5·85 μ (Found: C, 78·1; H, 10·1. $C_{17}H_{26}O_2$ requires C, 77·9; H, 9·9 per cent). By warming the $\beta:\gamma$-unsaturated ketone at 50° for 25 min with a 5 per cent solution of sodium in methanol only partial isomerisation to the $\alpha:\beta$-unsaturated ketone was achieved. The infra-red spectrum indicated a mixture of approximately equal parts of the two isomers, with bands at 2·95, 5·85 and 5·99 μ. This was also supported by the light absorption at 225 mμ ($\varepsilon = 7{\cdot}200$). (Found: C, 77·7; H, 10·1 per cent).

6-*Anisyl*-1-*hydroxy*-9-*methyl*-1:2:3:4:5:8:9:10-trans-*octahydronaphthalene* (IX)

9-Methyl-6-oxo-1-(2′-tetrahydropyranyloxy)-*trans*-decalin (1·2 g) and anisyl magnesium bromide (prepared from 540 mg magnesium and 4·2 g 4-bromoanisol in 25 cm³ anhydrous ether) were allowed to react as described previously for the corresponding *cis*-compound. The fraction of b.p. 200–210°/0·05 mm was warmed with aqueous ethanolic hydrogen chloride and the product isolated as usual. Crystallisation from ether—light petroleum gave colourless prisms (650 mg), m.p. 115° (Found: C, 79·6; H, 8·9. $C_{18}H_{24}O_2$ requires C, 79·5; H, 8·8 per cent).

Reduction. Lithium (2·5 g) was added to a stirred solution of this ether (550 mg) in tetrahydrofuran (50 cm³) and liquid ammonia (500 cm³); 10 min later ethanol (25 cm³) was dropped in slowly and after further 10 min the reaction mixture was decomposed with water and worked up as usual. The crude product (530 mg) was stirred under nitrogen at 0° with benzene (35 cm³) and 25 per cent sulphuric acid (50 cm³) for 10 min; the mixture was then warmed to 60°, kept at this temperature for 1 hr, and finally at room temperature for 12 hr. The sticky oil (500 mg) thus obtained was absorbed from light petroleum on neutral alumina (15 g); the fraction eluted with benzene—ether (9:1) gave an infra-red spectrum consistent with the structure of the $\beta:\gamma$-unsaturated ketone 6-(4′-*oxo*cyclo*hexenyl*)-9-*methyl*-trans-*decal*-1-*ol* (one intense band in the carbonyl region at 5·86 μ). The pale yellow oil was evaporatively distilled at a bath temperature of 220° at 0·2 mm (Found: C, 77·3, H; 10·2.

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$C_{17}H_{26}O_2$ requires C, 77·9; H, 9·9 per cent). The 2:4-*dinitrophenylhydrazone* crystallised from ethanol as yellow prisms, m.p. 108° (Found: C, 62·3; H, 6·8; N, 12·1. $C_{23}H_{30}O_5N_4$ requires C, 62·5; H, 6·8; N, 12·7 per cent). Treatment with warm sodium methoxide in methanol as described before for the corresponding *cis*-compound gave a mixture consisting of $\alpha:\beta$- and $\beta:\gamma$-unsaturated ketones. The infra-red spectrum had two bands in the carbonyl region at 5·86 and 5·99 μ. Light absorption: Max. 220 ($\varepsilon = 7000$).

6-*Anisyl*-1-*methoxy*-7:8-*dihydronaphthalene* (XII)

To an ice-cold ethereal suspension of anisyl magnesium bromide (prepared from 1·1 g magnesium and 9·5 g 4-bromoanisol in 50 cm³ ether) under nitrogen a solution of 1-methoxy-6-oxo-5:6:7:8-tetrahydronaphthalene (4 g) was added slowly with vigorous stirring. After 4 hr at room temperature and 4 hr refluxing ice and dilute sulphuric acid were added and the product isolated in the usual manner. Fractionation yielded an almost colourless oil (3·2 g), b.p. 175–185/0·2 mm which solidified and separated from ethanol in glistening, colourless platelets, m.p. 92–93° (Found: C, 81·1; H, 6·6. $C_{18}H_{18}O_2$ requires C, 81·2; H, 6·8 per cent).

6-(4′-*Oxo*cyclo*hexenyl*)-1-*methoxy*-5:6:7:8-*tetrahydronaphthalene* (XIII)

A fine white precipitate separated on addition of a solution of the above ether (1 g) in tetrahydrofuran (20 cm³) to liquid ammonia (300 cm³) and ethanol (60 cm³) but disappeared when sodium (6·8 g) in small pieces was added with vigorous stirring. The reaction mixture was decomposed and worked up as usual and the crude product stirred and boiled with 3 per cent sulphuric acid under nitrogen for 15 min. Ether extraction isolated an oil which crystallised from light petroleum as clusters of stout prisms (400 mg), m.p. 118–119° (Found: C, 79·7; H, 8·1. $C_{17}H_{20}O_2$ requires C, 79·7; H, 7·8 per cent). Light absorption: Max. 270 mμ ($\varepsilon = 1480$). The 2:4-*dinitrophenylhydrazone* formed with Brady's reagent and crystallised from ethyl acetate—ethanol as yellow prisms, m.p. 162° (Found: C, 63·5; H, 5·8; N, 13·1. $C_{23}H_{24}O_5N_4$ requires C, 63·2; H, 5·5; N, 12·8 per cent).

6-(4′-*Oxo*cyclo*hex*-2-*enyl*)-1-*methoxy*-5:6:7:8-*tetrahydronaphthalene* (XIV)

After warming the $\beta:\gamma$-unsaturated ketone (200 mg) from above for 25 min at 50° with a 3 per cent solution of sodium in methanol (20 cm³) a pale yellow oil was isolated by ether extraction which solidified on trituration with light petroleum; recrystallisation from ether—light petroleum gave colourless prisms, m.p. 112–114° (Found: C, 79·4; H, 8·2. $C_{17}H_{20}O_2$ requires C, 79·7; H, 7·8 per cent). Light absorption: Max. 225 mμ ($\varepsilon = 15{,}000$) and 270 mμ ($\varepsilon = 1560$). The 2:4-*dinitrophenylhydrazone* crystallised from ethyl acetate—ethanol as red needles, m.p. 178° (Found: C, 62·9; H, 5·4; N, 12·8. $C_{23}H_{24}O_5N_4$ requires C, 63·3; H, 5·5; N, 12·8 per cent).

6-(4′-*Ethylenedioxy*cyclo*hexenyl*)-1-*methoxy*-5:6:7:8-*tetrahydronaphthalene* (XV)

The ketone (XIII) (500 mg) was refluxed in benzene (50 cm³) with ethylene glycol (0·5 cm³) and a few crystals of toluene-*p*-sulphonic acid for 5 hr, using a Dean–Stark head. The cold solution was washed free of acid and dried. After evaporation of the solvent the residue (430 mg) distilled as a pale yellow thick oil, b.p. 165°/0·1 mm (Found: C, 76·6; H, 8·1. $C_{19}H_{24}O_3$ requires C, 76·0; H, 8·0 per cent).

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THE ORGANIC CHEMISTRY OF DEOXYNUCLEOSIDES AND DEOXYNUCLEOTIDES

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Abstract—The organic chemistry of the naturally occurring deoxynucleosides and their phosphate esters is reviewed.

THE chemistry of the degradation products of deoxyribonucleic acid has been somewhat neglected until recent years, largely due to the relative inaccessibility of the deoxyribonucleosides and their derivatives. To date there is no convenient method of preparing large quantities of the deoxyribonucleosides, though their isolation after enzymic digestion of polydeoxyribonucleotides has been somewhat simplified by the application of ion-exchange chromatography.[1]

Treatment of DNA with a pancreatic deoxyribonuclease produces a complex mixture which has been examined by Markham and Smith[2] using paper chromatography and paper electrophoresis, and by Sinsheimer[3] using ion-exchange chromatography. Both types of analysis indicate the presence of a number of different dinucleotides, together with tri- and higher-nucleotide material and in the case of Sinsheimer's results, some small amount of mononucleotide (ca. 1 per cent). Further degradation of this mixture using an intestinal phosphatase preparation[4] yields the deoxynucleosides, or if the monoesterase activity is inhibited, the deoxynucleotides. Carter[5] has shown these latter are not analogous to the ribonucleotides isolated ofter alkaline degradation of ribonucleic acid, in that all the deoxyribonucleotides isolated were smoothly dephosphorylated by a 5′-nucleotidase.

When DNA is treated with dilute acid under mild conditions, rupture of the purine glycosidic linkages occurs, to give a purine-free product, apurinic acid.[6] Under more vigorous conditions, however, acid hydrolysis of DNA gives rise to the 3′:5′-diphosphates of thymidine and deoxycytidine[7] together with some pyrimidine mononucleotide material (both 3′-and 5′-phosphates), dinucleoside triphosphate and larger pyrimidine nucleotide fractions.[8] Since the benzyl esters of the various deoxynucleotides are analogous in structure to deoxyribonucleic acid, their acid hydrolysis was investigated. Both deoxygaunosine-3′ benzyl phosphate and deoxyadenosine-3′ benzyl phosphate were rapidly hydrolysed to the respective purine and 2-deoxyribose-3-benzyl phosphate. This sugar derivative then decomposed to give monobenzyl

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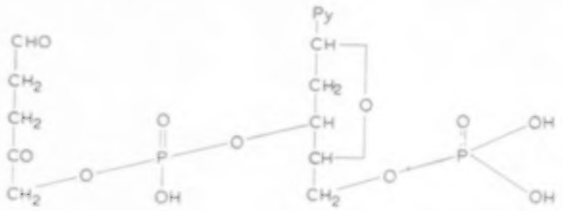
[1] W. Andersen, C. A. Dekker and A. R. Todd *J. Chem. Soc.* 2721 (1952).
[2] R. Markham and J. D. Smith *Biochim. Biophys. Acta* **8**, 350 (1952).
[3] R. L. Sinsheimer *J. Biol. Chem.* **208**, 444 (1954).
[4] W. Klein *Hoppe-Seyl. Z.* **207**, 125 (1932).
[5] C. E. Carter *J. Amer. Chem. Soc.* **73**, 1537 (1951).
[6] A. Kossel and A. Neumann *Ber. Dtsch. Chem. Ges.* **26**, 2753 (1893).
H. Bredereck and G. Müller *Ber. Dstch. Chem. Ges.* **72**, 115 (1939).
[7] C. A. Dekker, A. M. Michelson and A. R. Todd *J. Chem. Soc.* 947 (1953).
[8] A. M. Michelson and A. R. Todd Unpublished work; W. E. Cohn and E. Volkin *Biochim. Biophys. Acta* **24**, 359 (1957); S. K. Shapiro and E. Chargaff *Ibid.* **23**, 451 (1957).

phosphoric acid as the only identifiable product. Likewise the 2-deoxyribose-5-benzyl phosphate initially produced by the action of acid on deoxyadenosine-5′ benzyl phosphate, was hydrolysed to benzyl phosphoric acid. While the two monobenzyl phosphates of 2-deoxyribose were hydrolysed at different rates, the 3 isomer being more rapidly decomposed than the 5 compound, both were completely converted to monobenzyl phosphoric acid after 3 hr at 100° in 0·1 N HCl. Hydrolysis of the pyrimidine nucleotide benzyl esters followed quite a different pattern however. After even prolonged heating in 0·1 N HCl at 100°, the products from the 3′- and 5′-benzyl phosphates of thymidine and deoxycytidine were: unchanged benzyl ester, free nucleotide and only traces of other degradation products.[9] These results are in agreement with a mechanism involving preferential fission or elimination of the phosphate (β to an aldehyde group) from C_3 of the deoxyribose units flanking pyrimidine nucleotide residues or tracts, in the acid hydrolysis of apurinic acid.[10] It is known that acid treatment of 2-deoxyribose gives rise to ω-hydroxylaevulic aldehyde,[11] and this being the case, one might also expect ready fission of phosphate from C_5 due to the presence of the α-keto group.[12]

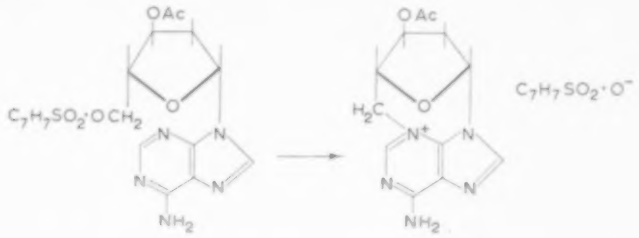


Some alternative fission of phosphoric acid from the pyrimidine nucleoside residue could also occur, giving rise to both 3′- and 5′-monophosphates of the pyrimidine nucleosides, via the 3:4 or 4:5 cyclic intermediates.[13]

Alkaline degradation of DNA has not been examined since Fischer[14] claimed to obtain oligonucleotide mixtures corresponding to 3·2–4·0 nucleotides in size, by the action of hot alkali. The stability of DNA towards alkali is of course the result of two factors (a) the phosphate linkage is stabilised by glycosidation of the sugar[15] and (b) lack of an OH group at C_2'.

[9] D. H. Hayes, A. M. Michelson and A. R. Todd Unpublished work.
[10] A. B. Foster, W. G. Overend and M. Stacey *J. Chem. Soc.* 980, 987 (1951); O. Meyerhof and K. Lohmann *Biochem. Z.* **271**, 98 (1934); D. M. Brown and A. R. Todd *The Nucleic Acids* (Edited by E. Chargaff and J. N. Davidson) Vol. 1, p. 409. Academic Press, New York (1955).
[11] R. E. Deriaz, M. Stacey, E. G. Teece and L. F. Wiggins *J. Chem. Soc.* 1222 (1949).
[12] P. Fleury, J. Courtois and A. Desjobert *Bull. Soc. Chim. Fr.* 694 (1948).
[13] C. Tam, H. S. Shapiro, R. Lipshitz and E. Chargaff *J. Biol. Chem.* **203**, 673 (1953).
[14] F. G. Fischer *Naturwissenschaften* **30**, 377 (1942).
[15] A. B. Foster, W. G. Overend and M. Stacey *J. Chem. Soc.* 987 (1951).

Since the deoxyribonucleosides do not contain an α-glycol system, the periodate oxidation method of Davoll *et al.*[16] cannot be used to establish the configuration of the glycosidic carbon atom. An independent proof of the β-configuration of the ribonucleosides however, lies in the discovery of the 5′-*cyclo*nucleosides derived from cytidine and adenosine.[17] Cyclisation from the 5′-position can only occur with a β-nucleoside; the preparation of *cyclo*nucleosides from deoxyadenosine and deoxycytidine thus provides a proof of their β-configuration. Treatment of 3′-acetyl deoxyadenosine with toluene-*p*-sulphonyl chloride gave a covalent toluene-*p*-sulphonyl derivative, which on heating in acetone, rearranged to the toluene-*p*-sulphonate of 3′-acetyl-2′-deoxy -3:5′ *cyclo*adenosine.[18]



The analogous 3′-acetyl 5′-toluene-*p*-sulphonyldeoxyguanosine could not be obtained. Treatment of 3′-acetyldeoxyguanosine with toluene-*p*-sulphonyl chloride, methane sulphonyl chloride and methane sulphonic anhydride was completely unsuccessful. Low reactivity of the hydroxyl groups in guanosine derivatives towards certain reagents has been previously observed. While 2′:3′-*iso*propylidene guanosine is readily acetylated and tritylated, toluene-*p*-sulphonylation could not be effected, and phosphorylation was successful only when phosphoryl chloride was used.[19]

Toluene-*p*-sulphonylation of N^6:3′-diacetyldeoxycytidine gave a covalent toluene-*p*-sulphonyl derivative, which was somewhat resistant to cyclisation, as would be expected, since the formation of *cyclo*nucleoside salts is to some extent dependent on the basic nature of the purine or pyrimidine residue, and N^6-acetylation of the cytosine residue might well prevent its occurrence. Deacetylation with cold methanolic ammonia gave 5′-toluene-*p*-sulphonyldeoxycytidine, which on heating in acetone solution, gave a complex mixture containing cytosine, toluene-*p*-sulphonate ion and sugar derivatives of unidentified nature. While the expected 3′-acetyl O^2:5′-*cyclo*deoxycytidine toluene-*p*-sulphonate was not isolated, the observation of toluene-*p*-sulphonate ion was a strong indication that an unstable *cyclo*nucleoside salt was formed, and that deoxycytidine is likewise to be regarded as a 2′-deoxy-β-D-ribofuranoside. It is likely that the positive charge on N_3, with a β—CH_2 group leads to instability of the N_3—C_1' linkage as well as the O_2—C_5' bond, thus giving complete fission of sugar from pyrimidine. Further evidence of the unstable character of the N_3—C_1' bond when a β—CH_2 is also present, is found in the behaviour of the *cyclo*thymidines—mild acid hydrolysis yields thymine—and not the nucleoside.[17] These *cyclo* derivatives, formation of which proves the β-configuration of thymidine, were first obtained from the

[16] J. Davoll, B. Lythgoe and A. R. Todd *J. Chem. Soc.* 833 (1946).
[17] V. M. Clark, A. R. Todd and J. Zussman *J. Chem. Soc.* 2952 (1951).
[18] W. Andersen, D. H. Hayes, A. M. Michelson and A. R. Todd *J. Chem. Soc.* 1882 (1954).
[19] A. M. Michelson and A. R. Todd *J. Chem. Soc.* 521 (1949); R. W. Chambers, J. G. Moffatt and H. G. Khorana *J. Amer. Chem. Soc.* **79**, 3747 (1957).

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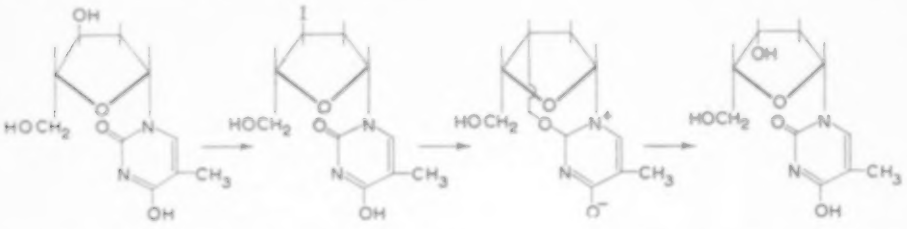
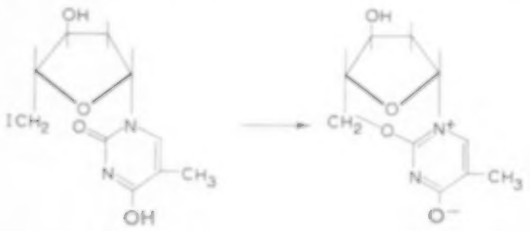
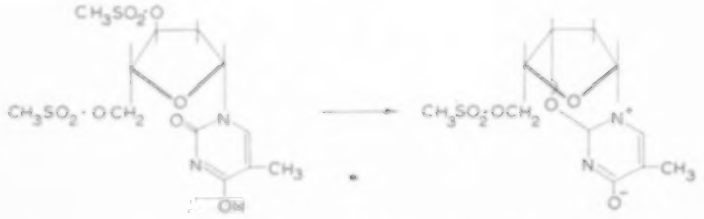
iodo-deoxythymidines. Treatment of 3′-iodo-3′-deoxythymidine with silver acetate in dry methyl cyanide containing a little base, yielded a highly crystalline compound, with however, none of the properties of the expected 3′-acetyl thymidine. Analysis and its physical properties indicated that it was a *cyclo*nucleoside. Acid hydrolysis gave thymine and 2-deoxyxylose, while alkaline hydrolysis gave thymine-3 β-D-2′-deoxy-xyloside, indicating inversion at C_3'.



Similarly 5′-iodo-5′-deoxythymidine yielded O^2-:5′-*cyclo*thymidine together with a little 5′-acetylthymidine, while cyclisation of 3′-acetyl-5′-iodo-5′-deoxythymidine gave the corresponding 3′-acetyl-O^2:5′-*cyclo*thymidine.[20]



Similar derivatives were obtained by the action of alcoholic ammonia on the 3′-sulphonyl derivatives—e.g. 3′:5′-dimethanesulphonyl thymidine gave 5′-methane-sulphonyl-O^2:3′-*cyclo*thymidine, the 5′-sulphonyl derivatives being quite stable under the conditions used.



Molecular models indicate that the ease of formation of these compounds is in the order $O^2{:}C^{3'} > O^2{:}C^{5'}$, the former involving inversion, and that in the ribose series an $O^2{:}C^{2'}$ cyclisation would be even more facile.[21]

The complete structure of thymidine as thymine 3-β-D-2′-deoxyribofuranoside has been confirmed by an X-ray crystallographic examination of 5′-bromo-5′-deoxythy-midine, by W. Cochran and M. Huber of the Cavendish Laboratory.

[20] A. M. Michelson and A. R. Todd *J. Chem. Soc.* 816 (1955).
[21] D. M. Brown, A. R. Todd and S. Varadarajan *J. Chem. Soc.* 2388 (1956).

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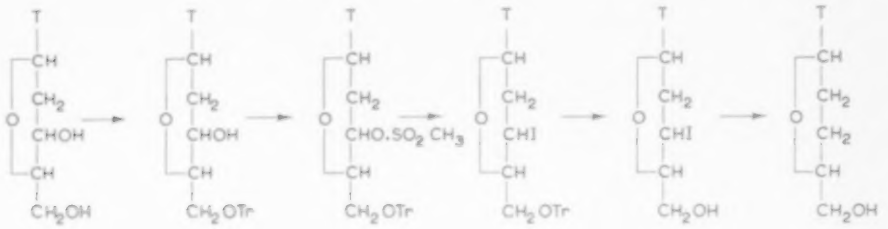
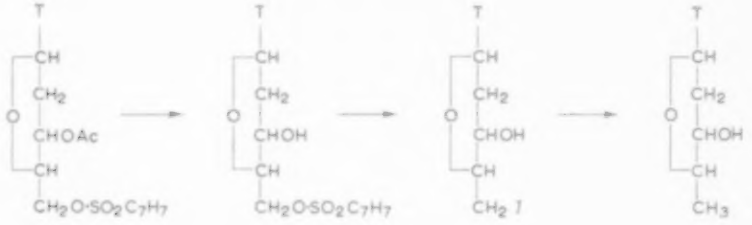
The preparation of the above-mentioned iodo-deoxythymidines and other derivatives is of some interest. Tritylation of thymidine under standard conditions gave 5′-tritylthymidine. On treatment with methane sulphonyl chloride, this yielded 3′-methanesulphonyl-5′-tritylthymidine which on heating with sodium iodide or lithium bromide in acetone, was converted to the 3′-halogeno-3′-deoxy-5′-tritylthymidine. Detritylation of 3′-iodo-3′-deoxy-5′-tritylthymidine gave 3′-iodo-3′-deoxythymidine, which was readily reduced by catalytic hydrogenation, to 3′-deoxythymidine.

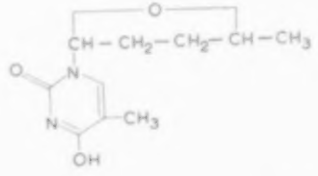


A similar series of reactions culminated in 5′-deoxythymidine. Acetylation of 5′-tritylthymidine followed by detritylation gave 3′-acetylthymidine, which was toluene-*p*-sulphonylated and the product deacetylated to give the highly crystalline 5′-toluene-*p*-sulphonylthymidine. Treatment with lithium bromide yielded 5′-bromo-5′- deoxythymidine, while sodium iodide produced 5′-iodo-5′-deoxythymidine, smoothly



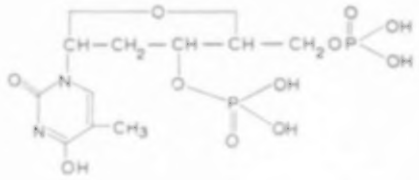
reduced to 5′-deoxythymidine. The 5′-deoxy- and 3′-deoxythymidines are of some interest as possible inhibitors of DNA metabolism.

Treatment of 3′:5′-dimethanesulphonylthymidine (obtained by methanesulphonylation of thymidine) with lithium bromide yielded 3′:5′-dibromo-3′:5′dideoxythymidine. Hydrogenation with a palladium–barium sulphate catalyst gave a monobromo derivative, shown to be 5′-bromo-3′:5′-dideoxythymidine, by an X-ray crystallographic examination of the compound, by Mr. M. M. Woolfson of the Cavendish Laboratory. Further hydrogenation gave 3′:5′-dideoxythymidine.



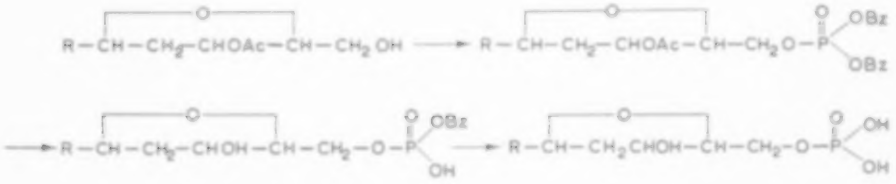
The fairly easy replacement of secondary sulphonyloxy groups by halogen, in these nucleoside derivatives is possibly due to the absence of the C_2'-hydroxyl group in the deoxyribonucleosides.

While the synthesis of the natural deoxynucleosides is as yet unreported,* the next step—phosphorylation of protected nucleosides to give the mononucleotides—has been completely achieved. Phosphorylation of thymidine with excess dibenzyl phosphorochloridate, followed by catalytic hydrogenation to remove benzyl groups, gave largely thymidine-3′:5′-diphosphate, together with some thymidine-5′-phosphate but no 3′-phosphate. The diphosphate, purified by ion exchange chromatography, or by boiling an aqueous solution of the dibarium salt, was identical in all respects with the product obtained by the acid hydrolysis of DNA.[7]



An analogous phosphorylation of deoxycytidine yielded deoxycytidine-3′:5′ diphosphate, though in rather small yield. The main product was deoxycytidine-5′-phosphate. As in the phosphorylation of thymidine, no 3′-phosphate was isolated, probably because under the conditions employed, the lower reactivity of the 3′-hydroxyl group (more pronounced in the case of deoxycytidine than in the case of thymidine) leads to the formation of 5′-phosphate which is then slowly phosphorylated at the 3′-position.

Thymidine-5′-phosphate was readily obtained from 3′-acetylthymidine. Phosphorylation with dibenzylphosphorochloridate gave 3′-acetylthymidine-5′-dibenzyl phosphate, which on alkaline treatment yielded thymidine-5′-benzylphosphate. Catalytic hydrogenation gave the nucleotide, identical with the natural material isolated from enzymic digests of DNA. This unambiguous synthesis is the final proof of the postulated structure for thymidylic acid.[22]



Thymidine-5′-phosphate can also be prepared by the preferential phosphorylation of thymidine, using dibenzyl phosphorochloridate.

The isomeric thymidine-3′-phosphate was prepared by phosphorylating 5′-trityl-thymidine and hydrolysing the product to thymidine-3′-benzyl phosphate, which on

* A recent communication by D. M. Brown, D. B. Parihar C. B. Reese and A. R Todd [*Proc. Chem. Soc.* 321 (1957)] describes the synthesis of 2′-deoxyuridine from 2′-toluene-*p*-sulphonyluridine, in excellent yield.

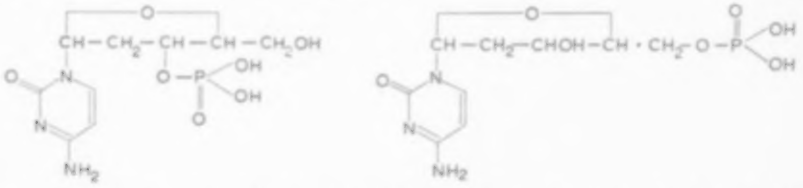
[22] A. M. Michelson and A. R. Todd *J. Chem. Soc.* 951 (1953).

hydrogenation, yielded thymidine-3′-phosphate, quite different from the natural nucleotide.

Like thymidine-3′:5′diphosphate, calcium and barium salts of thymidine-3′-phosphate are much more soluble in cold water than in hot, and both can be isolated by boiling an aqueous solution. This reverse solubility effect is not shown by salts of thymidine-5′-phosphate, and is seemingly characteristic of the 3′-position. Thymidine-5′-phosphate was also obtained by treating 3′-acetyl-5′-iodo-5′-deoxythymidine (obtained from 3′-acetyl-5′-toluene-*p*-sulphonylthymidine by the action of sodium iodide in acetone) with silver dibenzyl phosphate; protecting groups were removed from the product in the usual way.[20]

The isomeric thymidine mononucleotides can be distinguished by paper chromatography in a *n*-propanol (3 vol):2 N HCl (1 vol) system, or by ion exchange chromatography using Dowex-2 (formate form) and eluting with a solution of 0·01 M formic acid, 0·05 M with respect to sodium formate.

The deoxycytidine mononucleotides were prepared by analogous methods. Tritylation of deoxycytidine gave a very good yield of 5′-trityldeoxycytidine, which was phosphorylated with dibenzylphosphorochloridate. Acid hydrolysis of the crude product yielded deoxycytidine-3′-benzylphosphate, which was catalytically hydrogenated to deoxycytidine-3′-phosphate. Acetylation of 5′-trityldeoxycytidine yielded N^6:3′-diacetyl-5′-trityldeoxycytidine, which on acid hydrolysis gave a mixture of N^6:3′-diacetyldeoxycytidine, 3′-acetyldeoxycytidine and a little N^6-acetylcytosine. The diacetate was separated by counter-current distribution, phosphorylated and converted to deoxycytidine-5′-phosphate, identical with the nucleotide obtained by the action of DNAase and diesterase on DNA.[23]



The deoxycytidine mononucleotides can be conveniently separated by ion exchange chromatography on a Dowex-2 column (formate form) using 0·015 M formic acid as eluting solvent. As with the thymidylic nucleotides, the 5′-phosphate is eluted prior to the 3′-isomer.

The properties of the deoxycytidine phosphates are of considerable interest, due to their bearing on the orientation of the *a*- and *b*-ribonucleotides. A comparison of the infra-red spectra of the phosphates of deoxycytidine and cytidine provided strong evidence that cytidylic acid *b* is cytidine-3′-phosphate and hence that cytidylic acid *a* is the 2′-phosphate, a view which was further confirmed by a comparison of optical rotation and ultra-violet absorption data in the two series. Since uridylic acid *b* has

[23] A. M. Michelson and A. R. Todd *J. Chem. Soc.* **34** (1954).

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been prepared by deamination of cytidylic acid *b*, this evidence would apply equally to the orientation of uridylic acids *a* and *b*.

The problem of synthesis of the purine deoxynucleotides was complicated by the extreme instability of the purine deoxynucleosides and their derivatives to acid, and in the case of deoxyguanosine, by low reactivity of the nucleoside towards certain acylating agents. The methods adopted were however, essentially similar to those used for the pyrimidine deoxyribonucleotides.

Preparation of 3′-acetyldeoxyadenosine by tritylation of deoxyadenosine followed by acetylation and removal of the trityl group by hydrogenation gave such low yields (due to rupture of the glycosidic linkage) that the route was useless for preparative purposes. Partial acetylation of deoxyadenosine with acetic anhydride in pyridine, gave reasonable yields of the 3′- and 5′-monoacetates, separated from each other and from 3′:5′-diacetyldeoxyadenosine and unreacted deoxyadenosine by counter-current distribution. Comparison of the two monoacetates with the small amount of authentic 3′-acetyldeoxyadenosine available, identified the monoacetate obtained in smaller yield as 3′-acetyldeoxyadenosine and thus that the other was 5′-acetyldeoxyadenosine.[18] The two monoacetates were best prepared by partial deacetylation of 3′:5′-diacetyldeoxyadenosine, which gave a 60 per cent yield of the mixed monoacetates. With this method, the yield of monoacetate was fairly constant over a reasonable time base; variation occurred in the ratio of diacetylnucleoside to completely deacetylated nucleoside.[24]

Treatment of 3′-acetyldeoxyadenosine with dibenzylphosphoro chloridate in pyridine gave 3′-acetyldeoxyadenosine-5′-dibenzyl phosphate, which, with methanolic ammonia under suitable conditions, yielded deoxyadenosine-5′-benzyl phosphate. Removal of the benzyl group was effected by hydrogenolysis in aqueous solution, buffered to pH7 with sodium acetate to avoid fission of the glycosidic linkage. The deoxyadenosine-5′-phosphate so obtained was identical with that from natural sources.[21]

Phosphorylation of 5′-acetyldeoxyadenosine with dibenzyl phosphorochloridate was not satisfactory. However, with O-benzylphosphorous-O:O-diphenyl phosphoric anhydride,[25] the monoacetate gave a reasonable yield of 5′-acetyldeoxyadenosine-3′-benzyl phosphite. This was chlorinated with N-chlorosuccinimide and the nucleoside phosphorochloridate hydrolysed to 5′-acetyl-deoxyadenosine-3′-benzyl phosphate. Deacetylation and hydrogenolysis yielded deoxyadenosine-3′-phosphate, isolated as its calcium salt. The two deoxyadenosine phosphates were readily distinguished by ion exchange and paper chromatography.

For the synthesis of the corresponding deoxyguanosine phosphates, the isomeric monoacetates were prepared either by partial acetylation of deoxyguanosine, or by partial deacetylation of 3′:5′-diacetyldeoxyguanosine, the latter method being more convenient and also producing a better ratio of the two monoacetates. Since no reference compound corresponding to 3′-acetyl-5′-trityldeoxyadenosine was available, orientation of the two acetates was achieved by a direct comparison of the monoacetyldeoxyribose liberated on mild acid hydrolysis of 3′-acetyldeoxyadenosine, 5′-acetyldeoxyadenosine, and the two deoxyguanosine monoacetates. Differentiation of 3-acetyl-2-deoxyribose was possible by paper chromatography, in several solvent systems. Correspondence with the acetyldeoxyribose from each acetyl deoxyguanosine,

[24] D. H. Hayes, A. M. Michelson and A. R. Todd *J. Chem. Soc.* 808 (1955).
[25] N. S. Corby, G. W. Kenner and A. R. Todd *J. Chem. Soc.* 3669 (1952).

identified the monoacetate produced in larger amount as 5′-acetyldeoxyguanosine and the other as 3′-acetyldeoxyguanosine. An interesting observation noted during these experiments on the acid hydrolysis of the acetylated nucleosides, was the stabilising influence of sugar acetyl groups on the glycosidic linkage. Using 0·02 N hydrochloric acid at 100°, the results may be summarised as follows:

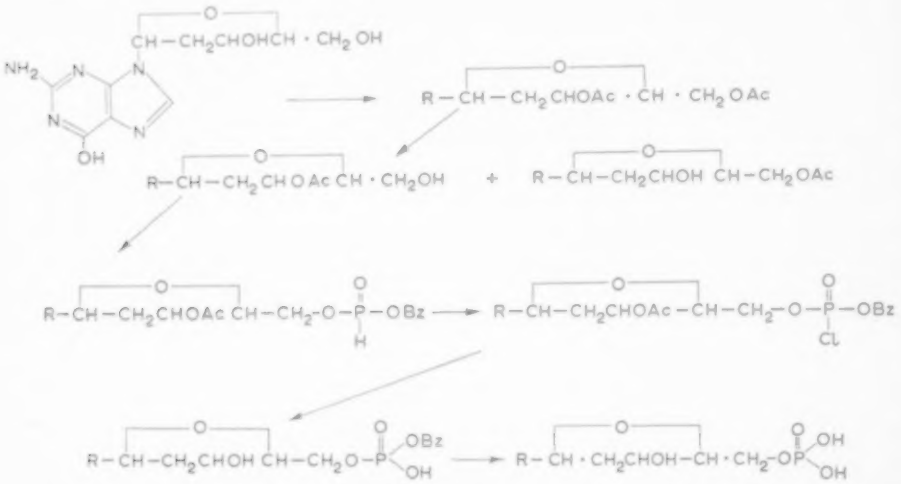
(1) The nucleosides are completely hydrolysed to purine and sugar after ca. 2 min.

(2) Glycosidic rupture of the monoacetyl nucleosides, independent of the position of the acetyl group in the sugar, is complete after 5 min.

(3) The glycosidic linkage in the 3′:5′-diacetyl derivatives is completely hydrolysed after 10 min, i.e. the effect of each acetyl group is approximately additive.

(4) Deoxyadenosine and its acetates are slightly more stable than the corresponding deoxyguanosine derivatives.

The two monoacetyldeoxyguanosines were phosphorylated with O-benzyl-phosphorous-O:O-diphenylphosphoric anhydride and the products converted to the corresponding nucleotides, by the methods described for the synthesis of deoxyadenosine-3′-phosphate.



The action of several enzymes on the deoxynucleotides and their esters was examined. Prostate monoesterase dephosphorylated all the mononucleotides (including thymidine-3′:5′-diphosphate), while rattlesnake (*Crotalus atrox*) venom dephosphorylated thymidine-5′-phosphate, deoxyadenosine-5′-phosphate, deoxycytidine-5′-phosphate, deoxyguanosine-5′-phosphate and their monobenzyl esters, but had no action on the corresponding 3′-phosphates and their benzyl esters or on thymidine-3′:5′-diphosphate and deoxycytidine-3′:5′-diphosphate. None of the compounds was affected by deoxyribonuclease or ribonuclease.[23]

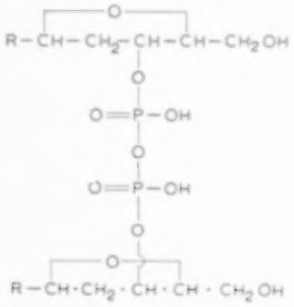
The next phase of synthetic nucleotide work was the synthesis of small polynucleotides for comparison with the natural nucleic acids and some of their larger breakdown products. Thymidine was acetylated and the resultant 3′:5′-diacetyl thymidine submitted to a partial deacetylation treatment with dilute methanolic ammonia. The products—thymidine, 5′-acetyl-thymidine, 3′-acetylthymidine and unchanged 3′:5′-diacetylthymidine—were separated by counter-current distribution, to give good

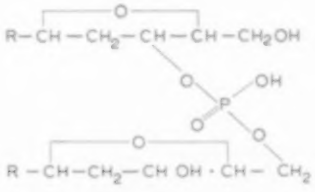
yields of the two monoacetates. The ratio of monoacetates formed was even more favourable than in the purine series, where a fairly marked selectivity is evident. Under optimum conditions for total monoacetate formation, the results may be summarised in Table 1:

TABLE 1

	Partial acetylation of nucleoside		Partial deacetylation of diacetyl nucleoside	
	% 5′-acetyl	% 3′-acetyl	% 5′-acetyl	% 3′-acetyl
Deoxyadenosine	73·5	26·5	66·0	34·0
Deoxyguanosine	90·6	9·4	66·6	33·4
Thymidine			57·0	43·0

Treatment of 5′-acetylthymidine with O-benzyl phosphorous-O:O-diphenylphosphoric anhydride yielded 5′-acetylthymidine-3′-benzyl phosphite. This was chlorinated with N-chlorosuccinimide to give 5′-acetylthymidine-3′-benzyl phosphorochloridate. While phosphorylation of 3′-acetylthymidine with 5′-acetylthymidine-3′-benzyl-P_1:P_2-diphenyl pyrophosphate (i.e. the mixed anhydride prepared from the phosphorochloridate and the triethylamine salt of diphenylphosphoric acid) or the trifluoroacetyl anhydride was unsuccessful, direct phosphorylation was achieved on treating 3′-acetylthymidine with 5′-acetylthymidine-3′-benzyl phosphorochloridate in the presence of base. After the removal of protecting groups from the crude product, a mixture containing thymidine-3′-phosphate, di(thymidine-3′)-P_1:P_2-pyrophosphate and thymidine-3′-thymidine-5′-phosphate, was obtained. Separation by ion-exchange chromatography gave the individual components.



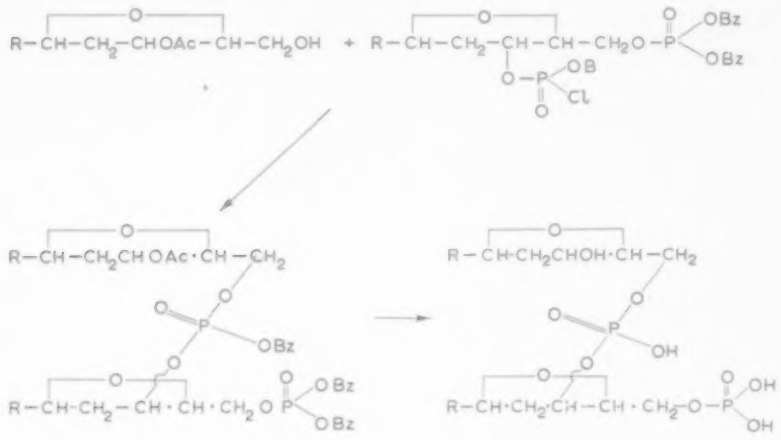


Dithymidine-3′-P_1:P_2-3′-pyrophosphate probably arises from slight hydrolysis of the nucleoside phosphorochloridate, to give the benzyl phosphate, which then rapidly reacts with the phosphorochloridate.

The synthesis of a true dinucleotide was accomplished by an analogous route.[25] Phosphorylation of 3′-acetylthymidine with dibenzyl phosphorochloridate yielded 3′-acetylthymidine-5′-dibenzylphosphate which was deacetylated and the thymidine -5′-dibenzylphosphate treated with O-benzyl phosphorous-O:O-diphenylphosphoric

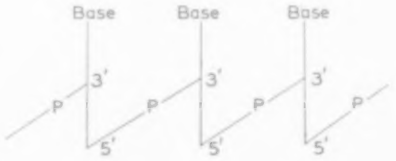
[25] A. M. Michelson and A. R. Todd *J. Chem. Soc.* 2632 (1955).

anhydride to give the 3′-phosphite. Chlorination gave thymidine-3′-benzylphosphochloridate-5′-dibenzyl phosphate, which was used to phosphorylate 3′-acetylthymidine in the presence of base, to give the fully protected dinucleotide. Acid hydrolysis to remove tertiary benzyl groups, followed by alkaline hydrolysis to remove the acetyl group yielded the monobenzyl dinucleotide. Catalytic hydrogenation gave 5′-phosphothymidine-3′-thymidine-5′-phosphate, isolated as its crystalline calcium salt. By-products of the reaction also isolated were thymidine-3′:5′-diphosphate and di-5′-phosphothymidine-3′-P_1:P_2-3′-pyrophosphate.



The various thymidine phosphates can be characterised by paper chromatography; a better method however, is paper electrophoresis in 0·1 M potassium dihydrogen phosphate and in 0·1 M disodium hydrogen phosphate. While the former solvent suppresses dissociation of secondary phosphoryl groups, so that migration is dependent on the number of primary dissociations only, (apart from the effect due to increase in molecular weight) with the alkaline system, both primary and secondary dissociations are of importance. Complete identification can therefore be established by running in both solvents.

As expected, purified prostate monoesterase removed the terminal phosphate from the dinucleotide, giving thymidine-3′-thymidine-5′-phosphate, identical with the material prepared synthetically. Similarly, dithymidine-3′:3′-P_1:P_2-pyrophosphate



was obtained from di(5′-phosphothymidine)3′-P_1:P_2-pyrophosphate. Purified rattlesnake venom diesterase split the synthetic thymidine-3′-thymidine-5′-phosphate to 1 mol. of thymidine and 1 mol. of thymidine-5′-phosphate, while the dinucleotide gave 2 mol. of thymidine-5′-phosphate only.

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These results are in accord with expectation and are in complete agreement with those obtained with solutions of dinucleotides prepared by enzymic degradation of DNA and so provide direct synthetic support for the structures assigned to them, and hence to the 3′:5′-linked polynucleotide structure of DNA.

The outstanding chemical problems in deoxyribonucleic acid work concern the synthesis of the naturally occurring deoxynucleosides, development of methods[27] for the synthesis of a number of purine and pyrimidine di- and tri-nucleotides, and the polymerisation of deoxynucleotides or nucleotide derivatives to a degree when the product could legitimately be called a deoxyribonucleic acid. As far as the gross molecule is concerned, a suitable method for the determination of sequence in the polynucleotide chain has yet to be devised.

[27] H. G. Khorana, W. E. Razzell, P. T. Gilham, G. M. Tener and E. H. Pol *J. Amer. Chem. Soc.* **79**, 1002 (1957).

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ELEMENTARY MOLECULAR ORBITAL TREATMENT OF *CYCLO*PROPANE AND *CYCLO*BUTANE

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Abstract—A theory of binding in *cyclo*propane and *cyclo*butane involving non-orthogonal orbitals is proposed. The theory accounts for the observed auxochromic effects in these molecules in a simple way, and correctly predicts several properties of these molecules.

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ONE of the unsatisfactory features of present-day MO theory is the artificiality of its treatment of *cyclo*propane.[1–6] It has long been known that it is impossible to form orthogonal *sp*-hybrids with bond angles of less than 90°, so that current treatments either do not overlap orbitals along the line of centres of carbon atoms, forming so-called "banana" bonds,[1] or else invoke a certain amount of π-bonding in this substance.[2] It is the feeling of the authors that, for some cases at least, the requirement of orthogonality is too stringent. If an MO is formed from LCAO's

$$\Psi = \Sigma a_{ij}\phi_{ij}$$

where ϕ_{ij} represents the jth AO on the ith atom, then this MO can be interpreted in terms of a bond additivity rule if the AO's on a given atom are orthogonal. If these AO's are not orthogonal, then the MO's so formed are not considered to represent localized bonds,[7] implying the failure of the bond additivity rule for the substance under discussion. Most chemical evidence indicates that bond additivity rules are quite accurate, so that it is reasonable to require orthogonality in most cases. There is, however, some disagreement in the literature as to the value of the C–C bond energy in[8,9] *cyclo*propane. Also, several workers have reported that the replacement of a double bond in a conjugated chain with a *cyclo*propyl group does not completely destroy effects characteristic of conjugation.[10,11] These observations are most easily discussed in terms of nonlocalized electrons, which in turn suggest, in the light of the foregoing, nonorthogonal orbitals. Theory demands the orthogonality of the solutions of Schroedinger's equation for the molecule, of course, but it is strictly speaking not necessary to demand orthogonality of the functions that go to make up the MO. Here they are conveniently described as having the form of AO's, but we shall carry over only those properties that are useful to us.

[1] T. M. Sugden *Nature, Lond.* **160,** 367 (1947).
[2] A. D. Walsh *Nature, Lond.* **159,** 164 (1947).
[3] R. Robinson *Nature, Lond.* **159,** 400 (1947).
[4] C. A. Coulson and W. E. Moffitt *J. Chem. Phys.* **15,** 151 (1947).
[5] C. A. Coulson and W. E. Moffitt *Phil. Mag.* **40,** 1 (1949).
[6] A. D. Walsh *Trans. Faraday Soc.* **45,** 179 (1949).
[7] C. A. Coulson *Valence.* Oxford Press (1952).
[8] F. H. Seubold *J. Chem. Phys.* **21,** 1616 (1953).
[9] H. O. Pritchard and A. F. Trotman-Dickenson *J. Chem. Phys.* **22,** 944 (1954).
[10] G. W. Perold *J. S. Afr. Chem. Inst.* **6,** 22 (1953).
[11] J. J. Wren *J. Chem. Soc.* 2208 (1956).

Cyclo*propane*

Let us drop the orthogonality requirement for the orbitals that will be used to form C–C bonds and substitute it its place the requirement that the orbitals have maximum bond forming power in the Pauling sense. This latter is suggested, but in no way established, by the fact that the C–C bond length in *cyclo*propane, 1·526 Å,[12] is very close the normal C–C bond length. We form four *sp*-hybrids distributed as follows: two equivalent orbitals in the *xz*-plane, each making an angle of 30° with the $+x$ axis, to be used in forming C–C bonds, and two equivalent orbitals in the *xy*-plane making equal, but not necessarily 30°, angles with the $-x$ axis. For the first and second orbitals, we require a bond forming power, *F*, of 2. For the third and fourth, we require mutual orthogonality and also orthogonality with the first and second. The required AO's are

$$\phi_a = \frac{1}{2}s + \frac{3}{4}p_x + \frac{\sqrt{3}}{4}p_z$$

$$\phi_b = \frac{1}{2}s + \frac{3}{4}p_x - \frac{\sqrt{3}}{4}p_z$$

$$\phi_c = \frac{3}{\sqrt{26}}s - \frac{\sqrt{2}}{\sqrt{13}}p_x + \frac{1}{\sqrt{2}}p_y$$

$$\phi_d = \frac{3}{\sqrt{26}}s - \frac{\sqrt{2}}{\sqrt{13}}p_x - \frac{1}{\sqrt{2}}p_y$$

It is seen that ϕ_a and ϕ_b are the first pair mentioned above, and ϕ_c and ϕ_d are the second pair.

Two items of immediate interest are the *F* of ϕ_c and ϕ_d, and the H–C–H angle, 2η (Fig. 1). A straight forward calculation of F_c or F_d gives

$$F_c = F_d = \frac{3}{\sqrt{26}} - \frac{\sqrt{2}}{\sqrt{13}}\sqrt{3}(1) - \frac{\sqrt{2}}{\sqrt{17}} + \frac{1}{\sqrt{2}}3\ (1)\ \frac{\sqrt{13}}{\sqrt{17}} = 1{\cdot}988$$

close to the usual value of 2; $\tan\eta$ is given by the coefficient of p_y divided by the coefficient of p_x in ϕ_c.

$$\tan\eta = \frac{1/\sqrt{2}}{\sqrt{2}/\sqrt{13}} = \frac{\sqrt{13}}{2}$$

$$\eta = 61°$$

$$2\eta = 122°$$

This value is to be compared with 118·2° ± 2·0° found by Bastiansen and Hassel[13] using electron diffraction techniques. A later value is reported by Günthard *et al.*[14] as being just above 120°. The treatment of Coulson referred to above yields $F = 1{\cdot}883$ and an H–C–H angle of 116°.[5]

[12] L. Pauling and L. O. Brockway *J. Amer. Chem. Soc.* **59**, 1223, (1937).
[13] O. Bastiansen and O. Hassel *Tidsskr. Kemi. Bergv.* **6**, 71 (1946).
[14] H. H. Günthard, R. C. Lord and T. K. McCubbin, Jr. *J. Chem. Phys.* **25**, 768 (1956).

Since it is not immediately clear how the interaction of nonorthogonal orbitals will affect the energy of our system, we next set up the MO's for the C–C bonds. Labelling the orbitals as indicated in Fig. 2, we have

$$\Psi = C_{1a}\phi_{1a} + C_{1b}\phi_{1b} + C_{2a}\phi_{2a} + \cdots + C_{2b}\phi_{2b}.$$

By symmetry, and using the usual notation and assumptions,

$$H_{1a,1a} = H_{1b,1b} = \ldots = H_{2b,2b} = Q \qquad S_{1a,1a} = \ldots = S_{2b,2b} = 1$$
$$H_{1a,2b} = H_{2a,3b} = H_{3a,1b} = \beta \qquad S_{1a,2b} = S_{2a,3b} = S_{3a,1b} = 0$$
$$H_{1a,1b} = H_{2a,2b} = H_{3a,3b} = X \qquad S_{1a,1b} = S_{2a,2b} = S_{3a,3b} = J$$

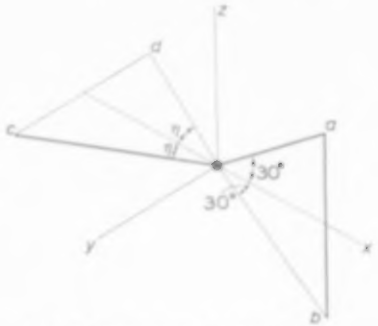


FIG. 1. Disposition of orbitals about carbon atoms in *cyclo*propane.

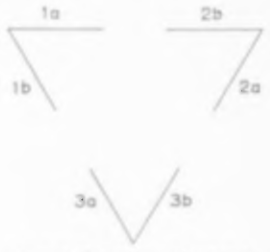


FIG. 2. Labelling of orbitals in *cyclo*propane ring.

All other H's and S's are zero. A straightforward calculation of J from the angular parts of the wave functions, permissible because of the assumed identity of the radial parts, gives $J = 5/8$. X, the corresponding Hamiltonian integral could likewise be evaluated directly, but for simplicity we shall assume $X = JQ$. (See Appendix II.) Setting $Q - E = W$, we have the secular equation

$$\begin{vmatrix} W & \beta & 0 & 0 & 0 & JW \\ \beta & W & JW & 0 & 0 & 0 \\ 0 & JW & W & \beta & 0 & 0 \\ 0 & 0 & \beta & W & JW & 0 \\ 0 & 0 & 0 & JW & W & \beta \\ JW & 0 & 0 & 0 & \beta & W \end{vmatrix} = 0 \qquad (1)$$

This equation may be solved in a variety of ways. (See Appendix I.) The six roots are

$$E_{a+} = E_{a-} = Q + 1{\cdot}9\beta$$
$$E_{0+} = Q + 0{\cdot}62\beta$$
$$E_{\beta+} = E_{\beta-} = Q - 0{\cdot}87\beta$$
$$E_{0-} = Q - 2{\cdot}7\beta$$

Putting six electrons into the three lowest levels and remembering that $\beta < 0$, we find for the total energy

$$E_t = 6Q + 8{\cdot}8\beta$$

A treatment with orthogonal AO's is the same as above with $J = 0$ and β replaced with β'. The determinant now factors, giving three roots $W = \beta'$ and three $W = -\beta'$. The total energy is $6\ W + 6\ \beta'$. Since it is clear that the absolute value of β is a maximum for orbitals that overlap under the best possible conditions, we conclude, to this approximation, that the treatment using nonorthogonal orbitals leads to a somewhat improved energy. A fuller discussion would call attention to the increased interelectronic repulsion and kinetic energy associated with the confinement of the electrons more strictly to the ring. To a considerable extent these are offset by the enhancement of the coulombic attraction and the overlap just mentioned. Appendix II carries the discussion a bit further.

Cyclo*butane*

A similar treatment for cyclobutane can be carried through, assuming 90° instead of 60° orbitals. The four LCAO's for carbon are

$$\phi_a = \frac{1}{2}s + \frac{\sqrt{3}}{\sqrt{8}}p_x + \frac{\sqrt{3}}{\sqrt{8}}p_z$$

$$\phi_b = \frac{1}{2}s + \frac{\sqrt{3}}{\sqrt{8}}p_x - \frac{\sqrt{3}}{\sqrt{8}}p_z$$

$$\phi_c = \frac{\sqrt{3}}{\sqrt{10}}s - \frac{1}{\sqrt{5}}p_x + \frac{1}{\sqrt{2}}p_y$$

$$\phi_d = \frac{\sqrt{3}}{\sqrt{10}}s - \frac{1}{\sqrt{5}}p_x - \frac{1}{\sqrt{2}}p_y$$

Again, the first pair refer to C–C bonds and the second to H–C bonds. As before, we may calculate $F_2 = 1{\cdot}997$ and an H–C–H angle of 115°. Using the same notation as before, $S_{1a,1a} = J = 1/4$. Again solving the secular equation under the same assumptions as before, we find a total energy of $8\ Q + 8{\cdot}2\ \beta$ as compared to $8\ Q + 8\ \beta'$ for the treatment with orthogonal orbitals. The conclusion here is that conjugation is much less important for an interposed *cyclo*butyl group than it is for a *cyclo*propyl group. Recently Wren[11] has measured an auxochromic effect for *cyclo*butyl. The results bear out the above.

*Chloro*cyclo*propane*

It is of interest to see how orbitals of this type can be used to describe the observations that chloro*cyclo*propane is very difficult to hydrolyze.[15] Brown *et al.*[16] have explained this by noting that the strain in the transition state, represented by a carbonium ion with the hydrogen atom in the plane of the ring, is even greater than that of the initial state. Let us form such an orbital and calculate its F.

Taking ϕ_a and ϕ_b as before for *cyclo*propane, we now require ϕ_c along the $-x$ axis, orthogonal to ϕ_a and ϕ_b and normalized. Such an orbital is

$$\phi_c = \frac{3}{\sqrt{13}}s - \frac{2}{\sqrt{13}}p_x$$

[15] J. D. Roberts and V. C. Chambers *J. Amer. Chem. Soc.* **73**, 5030 (1951).
[16] H. C. Brown, R. S. Fletcher and R. B. Johannesen *J. Amer. Chem. Soc.* **73**, 212 (1951).

For this orbital, $F = 1{\cdot}793$, considerably less than the F of the orbital out of which it is formed in the course of the reaction. Since the transition state involves not only the removal of a chloride ion, but also the weakening of a C–H bond, we conclude that the energy requirements of the transition state are very high and the reaction should proceed very slowly, as indeed it does.

APPENDIX I

Factoring of the secular equation

Equation (1) of the text may be factored by using symmetry orbitals (SO's) rather than the $\phi_{ia,b}$ as basis functions. Determination of the SO's is straightforward using either group theory[17] or alternative methods which do not use explicitly the formalism of group theory.[18]

In determining the SO's we need not employ the full symmetry, since we are concerned only with bonds in the plane of the carbon ring. Thus we use the symmetry group C_{3v} for *cyclo*propane and C_{4v} for *cyclo*butane. We consider first *cyclo*propane.

To find the SO's we must diagonalize appropriate symmetry operators.[18] For *cyclo*propane we can conveniently form SO's which diagonalize the rotations about the threefold axis by taking the linear combinations:

$$\chi = \sum_{k=1}^{3} \epsilon^{-(k-1)j}\, \phi_{ka,b} \qquad (j = 0, \pm 1, \dots) \tag{1}$$

where $\epsilon^j = \exp j\,(i\,2\pi/p)$, $p =$ order of rotation (in this case 3). For $j = 0$ we have two linear combinations $\phi_{1a} + \phi_{2a} + \phi_{3a}$, $\phi_{1b} + \phi_{2b} + \phi_{3b}$. For $j = 0$, however, another set of symmetry operations, the reflections in the three vertical planes passing through the symmetry axis and the three carbon atoms, may simultaneously be diagonalized. The pair of functions above may be added and subtracted to give SO's which belong to $j = 0$ and are, respectively, symmetric (+) and anti-symmetric (−) with respect to reflections:

$$\chi_{0+} = \frac{1}{N_1}\left[(\phi_{1a} + \phi_{1b}) + (\phi_{2a} + \phi_{2b}) + (\phi_{3a} + \phi_{3b})\right] \tag{2}$$

$$\chi_{0-} = \frac{1}{N_2}\left[(\phi_{1a} - \phi_{1b}) + (\phi_{2a} - \phi_{2b}) + (\phi_{3a} - \phi_{3b})\right] \tag{3}$$

The normalizing factors N_1 and N_2 are:

$$N_1 = \sqrt{6(1 + J)}$$

$$N_2 = \sqrt{6(1 - J)}$$

For $j = +1$, we obtain a number of SO's depending on which carbon atom we choose as the initial one in the sum (1), but the only essentially different ones are:

$$\chi_1 = \frac{1}{N_1}\left[(\phi_{1a} + \phi_{1b}) + \gamma^*(\phi_{2a} + \phi_{2b}) + \gamma(\phi_{3a} + \phi_{3b})\right] \tag{4a}$$

$$\chi'_1 = \frac{1}{N_2}\left[(\phi_{1a} - \phi_{1b}) + \gamma^*(\phi_{2a} - \phi_{2b}) + \gamma(\phi_{3a} - \phi_{3b})\right] \tag{4b}$$

$$\gamma = e^{2\pi i/3}$$

[17] M. A. Melvin *Rev. Mod. Phys.* **28**, 18 (1956).

[18] John C. Slater *Electronic Structure of Atoms and Molecules.* Technical Report No. 3, Solid-State and Molecular Theory Group, Massachusetts Institute of Technology, Cambridge, Massachusetts.

These functions do not have the property of being either symmetric or antisymmetric with respect to reflections. Indeed reflection in the plane through carbon atom 1 converts (4a) and (4b) respectively into

$$\chi_{-1} = \frac{1}{N_1}[(\phi_{1a} + \phi_{1b}) + \gamma(\phi_{2a} + \phi_{2b}) + \gamma^*(\phi_{3a} + \phi_{3b})] \tag{5a}$$

$$\chi'_{-1} = -\frac{1}{N_2}[(\phi_{1a} - \phi_{1b}) + \gamma(\phi_{2a} - \phi_{2b}) + \gamma(\phi_{3a} - \phi_{3b})] \tag{5b}$$

where, as the notation indicates, χ_{-1} and χ'_{-1} are the symmetry orbitals obtained by substituting $j = -1$ into (1). We conclude that χ_1 and χ_{-1} are degenerate as are χ'_1 and χ'_{-1}.

Using these symmetry orbitals as our basis functions rather than the atomic orbitals $\phi_{1a,b}$, we conclude that χ_{0+} and χ_{0-} are already MO's, since they can combine only with SO's having the same symmetry and there are no other such linearly-independent SO's formed from the $\phi_{ia,b}$. However, χ_1 and χ'_1 do have the same symmetry and yield a quadratic secular equation; χ_{-1} and χ'_{-1} give the same quadratic equation. The correct linear combinations are of the form

$$\left.\begin{aligned} &\sqrt{1-\delta^2}\,\chi_1 - i\,\delta\,\chi'_1 \\ &\sqrt{1-\delta^2}\,\chi_{-1} + i\,\delta\,\chi'_{-1} \end{aligned}\right\} E_{\alpha\pm}$$

$$\left.\begin{aligned} &i\,\delta\chi_1 - \sqrt{1-\delta^2}\,\chi'_1 \\ &i\,\delta\chi_{-1} + \sqrt{1-\delta^2}\,\chi'_{-1} \end{aligned}\right\} E_{\beta\pm}$$

where δ is a numerical coefficient. By adding and subtracting the degenerate pairs we can obtain the MO's in real form. In this form the functions have the property of being either symmetric or antisymmetric to reflection in the plane passing through carbon atom 1.

We list the molecular orbitals so obtained along with those of equations (2) and (3) thereby obtaining the complete set of six orbitals for *cyclo*propane. They are in order of increasing energy:

$$\left.\begin{aligned} \Psi_{\alpha+} &= -0{\cdot}21(\phi_{1a} + \phi_{1b}) + 0{\cdot}83(\phi_{2a} + \phi_{2b}) - 0{\cdot}62(\phi_{3a} + \phi_{3b}) \\ \Psi_{\alpha-} &= -0{\cdot}84(\phi_{1a} - \phi_{1b}) + 0{\cdot}24(\phi_{2a} - \phi_{2b}) - 0{\cdot}60(\phi_{2b} - \phi_{3a}) \end{aligned}\right\}$$

$$\Psi_{0+} = \frac{1}{3{\cdot}1}[(\phi_{1a} + \phi_{1b}) + (\phi_{2a} + \phi_{2b}) + (\phi_{3a} + \phi_{3b})]$$

$$\left.\begin{aligned} \Psi_{\beta+} &= 0{\cdot}40(\phi_{1a} + \phi_{1b}) + 0{\cdot}17(\phi_{2a} + \phi_{2b}) - 0{\cdot}57(\phi_{3a} + \phi_{2b}) \\ \Psi_{\beta-} &= -0{\cdot}43(\phi_{1a} - \phi_{1b}) + 0{\cdot}56(\phi_{2a} - \phi_{2b}) + 0{\cdot}13(\phi_{2b} - \phi_{3a}) \end{aligned}\right\}$$

$$\Psi_{0-} = \frac{1}{1{\cdot}5}[(\phi_{1a} - \phi_{1b}) + (\phi_{2a} - \phi_{2b}) + (\phi_{3a} - \phi_{3b})]$$

The bracketed functions are degenerate pairs.

The procedure for *cyclo*butane is similar except that the treatment of C_{4v} symmetry is in some respects simpler. The MO's are in order of increasing energy:

$$\Psi^*_{0+-} = \frac{1}{\sqrt{6}}[(\phi_{1a} - \phi_{1b}) - (\phi_{2a} - \phi_{2b}) + (\phi_{3a} - \phi_{3b}) - (\phi_{4a} - \phi_{4b})]$$

$$\left.\begin{aligned}\Psi^*_{x+} &= 0{\cdot}51(-\phi_{1a} - \phi_{2b} + \phi_{3a} + \phi_{4b}) + 0{\cdot}07(\phi_{1b} + \phi_{2a} - \phi_{3b} + \phi_{4a})]\\ \Psi^*_{x-} &= 0{\cdot}07(-\phi_{1a} + \phi_{2b} + \phi_{3a} - \phi_{4b}) + 0{\cdot}51(\phi_{1b} - \phi_{2a} - \phi_{3b} + \phi_{4a})]\end{aligned}\right\}$$

$$\Psi^*_{0++} = \frac{1}{\sqrt{10}}[(\phi_{1a} + \phi_{1b}) + (\phi_{2a} + \phi_{2b}) + (\phi_{3a} + \phi_{3b}) + (\phi_{4a} + \phi_{4b})]$$

$$\Psi^*_{0-+} = \frac{1}{\sqrt{10}}(\phi_{1a} + \phi_{1b}) - (\phi_{2a} + \phi_{2b}) + (\phi_{3a} + \phi_{3b}) - (\phi_{4a} + \phi_{4b})]$$

$$\left.\begin{aligned}\Psi^*_{\beta+} &= 0{\cdot}07(\phi_{1a} + \phi_{2b} - \phi_{3a} - \phi_{4b}) + 0{\cdot}51(-\phi_{1b} - \phi_{2a} + \phi_{3b} + \phi_{4a})\\ \Psi^*_{\beta-} &= 0{\cdot}51(\phi_{1a} - \phi_{2b} - \phi_{3a} + \phi_{4b}) + 0{\cdot}07(-\phi_{1b} + \phi_{2a} + \phi_{3b} - \phi_{4a})\end{aligned}\right\}$$

$$\Psi^*_{0--} = \frac{1}{\sqrt{6}}[(\phi_{1a} - \phi_{1b}) + (\phi_{2a} - \phi_{2b}) + (\phi_{3a} - \phi_{3b}) + (\phi_{4a} - \phi_{4b})]$$

APPENDIX II

Approximations

Several matters touched upon in the main text deserve a somewhat extended discussion. Probably the most important such point is the assumption of $F = 2$ for the orbitals a and b. The necessity for a new assumption arises, of course, from the abandonment of orthogonality, which, in effect, had fixed one constant of the problem. Fig. 3 is a graph of various parameters of the system against F for orbital a or b. It is seen that, while the bond forming strength of orbitals c and d varies only slowly in the region of interest with F_a, the H–C–H angle, 2η varies quite rapidly. J is also seen to vary, though not sufficiently rapidly to vitiate the general argument. On the basis of this, then F_a was chosen to be 2. Any change in the measured H–C–H angle, necessitating a change in F_a, would cause only insignificant changes in the other parameters.

Another item requiring some justification is the assumption $X = JQ$. We may write the one electron Hamiltonian for the system as

$$H = H^1 + K$$

where H^1 is the atomic Hamiltonian for atom 1 and K is the coulombic effect of the other two centers. K is even with respect to the XY plane and negative everywhere. Now

$$H^1\phi_{1a} = E^1\phi_{1a}$$

$$H^1\phi_{1b} = E^1\phi_{1b}$$

as ϕ_{1a} and ϕ_{1b} are assumed to be degenerate solutions of the atomic problem. Multiply both of the equations by ϕ^*_{1a}, and integrate

$$\int\phi^*_{1a}H^1\phi_{1a} = E^1$$

$$\int\phi^*_{1a}H^1\phi_{1b} = E^1\int\phi^*_{1a}\phi_{1b} = JE^1$$

We require

$$\int \phi_{1a}^{*} H \phi_{1a} = E^1 + K_{1a,1a} = Q$$

and

$$\int \phi_{1a}^{*} H \phi_{1b} = JE^1 + K_{1a,1b} = X$$

Eliminating E^1,

$$X = JQ + K_{1a,1b} - JK_{1a,1b}$$

Since $K_{1a,1a}$ and $K_{1a,1b}$ have the same sign and are of the same order of magnitude, we expect $|K_{1a,1b} - JK_{1a,1a}| \sim |K_{1a,1b}|$, so that the approximation is almost certainly not any more serious for the non-orthogonal case than for the orthogonal. In

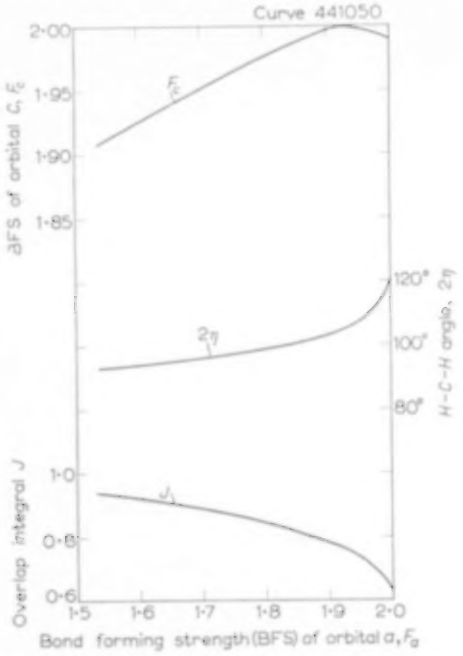


FIG. 3. Various atomic parameters of *cyclo*propane.

calculating the improvement caused by the abandonment of orthogonality, the error should roughly subtract out.

A final point concerning non-orthogonality. It may be shown that the energy calculated in the fashion usually employed in these very simple MO pictures decreases without limit as $J \to 1$, that is, as overlap becomes complete. The fault lies in the fact that the usual procedure of putting two electrons into each state implies a product wave function, whereas we know that the Pauli Principle does not permit simple product functions. The state of affairs here may be easily seen by referring to Appendix I. As $J \to 1$, we are left only three linearly independent AO's rather than six, so that we may form only three MO's. The SO's χ_{0-}, χ_1^1, and χ_{-1}^1 approach zero so that $\Psi_{g+}^{*} \to \Psi_{g-}^{*}$, $\Psi_{\beta+}^{*} \to \Psi_{\beta-}^{*}$, and $\Psi_{0-}^{*} \to 0$. Since we are dealing with the three lowest states, E_{g+}, E_{g-}, and E_{0+}, a determinant constructed out of these functions would vanish as $J \to 1$. In other words, the Pauli Principle would not permit the "catastrophe" to take place.

Tetrahedron, 1958, Vol. 2, pp. 353–360. Pergamon Press Ltd., London

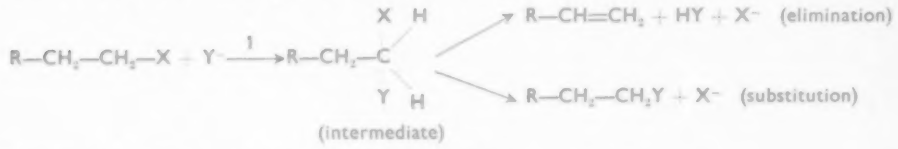
Vol. 2 1958

NOTES

An example of merged bimolecular substitution and elimination

(*Received* 5 *August* 1957)

WINSTEIN, DARWISH and HOLNESS[1] have recently postulated the existence of a new mechanism of simultaneous S_N2 and E_2 reactions which they call "merged bimolecular substitution and elimination". The mechanism may be schematized as follows:



Presumably formation of the intermediate (step 1) is rate-determining.

In an investigation which we are undertaking with different ends in mind, we have found evidence in support of the merged mechanism. When 4,4-dimethyl*cyclo*hexyl tosylate (I) was treated with sodium thiophenolate in 87% ethanol and the reaction followed acidimetrically, an overall second-order rate constant ($k_s + k_e$) of 19·04 (all rate constants given in l. mole^{-1} sec^{-1} × 10^5) was found. Iodimetric titration during reaction indicated that the entire* rate was due to substitution, i.e. $k_s = 19{\cdot}04$ and $k_e = 0$. This result should be contrasted with one for the parent compound *cyclo*hexyl tosylate (II) where the reaction with thiophenolate proceeded at an overall specific rate $k_s + k_e$ of 18·35, of which however only part was substitution ($k_s = 10{\cdot}09$) and part was elimination ($k_e = 8{\cdot}26$).[2] The agreement of the overall rate constants ($k_s + k_e$) was at first sight reasonable, since I and II exist at about the same equilibrium mixture of equatorial and axial conformations (with respect to the tosylate grouping) (Fig. 1) and the feebly electron-donating methyl groups should have no appreciable polar affect at the remote 4-position of the ring.[3,4†] The difference in the individual rate constants k_s and k_e is, however, at first sight surprising. One can perhaps understand why elimination in I is slower than in II, since in I the axial hydrogens at C_2 are shielded from attack by base by the axial

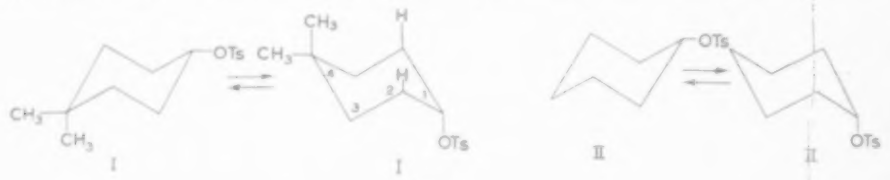


FIG. 1.

methyl at C_4. Indeed, we have found that the rate of bimolecular elimination for I with sodium ethoxide in absolute ethanol (0·349) is less than that for II (0·570) and the difference is magnified for the more bulky[5] base potassium *t*-butoxide in *t*-butanol (0·310 vs. 0·823). As thiophenolate may well

* The accuracy of the method is such that if more than 5–10 per cent of the total reaction had been elimination, it would have been detected.

† *Cyclo*hexanol and 4,4-dimethyl*cyclo*hexanol are acetylated at the same rate with acetic anhydride in pyridine.

[1] S. Winstein, D. Darwish and N. J. Holness *J. Amer. Chem. Soc.* **78**, 2915 (1956).
[2] E. L. Eliel and R. S. Ro *Chem. & Ind. (Rev.)* 251 (1956); *J. Amer. Chem. Soc.* **79**, 5995 (1957).
[3] J. F. J. Dippy, S. R. C. Hughes and J. W. Laxton *J. Chem. Soc.* 4102 (1954).
[4] E. L. Eliel and C. A. Lukach *J. Amer. Chem. Soc.* **79**, 5986 (1957).
[5] H. C. Brown and I. Moritani *J. Amer. Chem. Soc.* **75**, 4112 (1953); H. C. Brown, I. Moritani and Y. Okamoto *Ibid.* **78**, 2193 (1956).

have an even larger steric requirement than *t*-butoxide, the very slow elimination rate of I with this base is explained. It is not clear, however on the basis of the classical[6] S_N2-E_2 dichotomy why the *decrease* in elimination rate for I should lead to a corresponding *increase* in substitution rate so as to keep the overall rate approximately the same as for *cyclo*hexyl tosylate. On the basis of the merged mechanism[1] the interpretation is clear: The rate determining step I (equation above) proceeds at the same rate for I and II, but whereas the intermediate from II is converted partly to elimination and partly to substitution product, the intermediate from I gives substitution product exclusively (or nearly so) since elimination is sterically prevented. It is implied in this view that the product determining step in the merged mechanism involves attack by external base in so far as formation of the elimination product is concerned.

The merged mechanism implies that the rate-determining and product-determining steps are discrete. There are many instances in which this is not the case,[6] hence the merged mechanism cannot be general. It has been implied,[1] (and the present results seem to support this) that the merged mechanism is likely to be observed with strong nucleophiles of feebly basic properties, such as bromide and thiophenolate. The operation of the merged mechanism may be responsible for the remarkably high elimination rates observed in the reaction of *cyclo*hexyl tosylate,[2] *cis*-4-*t*-butyl*cyclo*hexyl tosylate[2] and *t*-butyl chloride[7] with sodium thiophenolate.

The present results are in good agreement with those obtained in the reaction of $(CH_3)_2CDCHOTsCH_3$ with bromide ion by Winstein *et al.*[8]

EXPERIMENTAL*

4,4-*Dimethylcyclohexyl tosylate* prepared from the parent alcohol[9] by the method of Tipson,[9] was a liquid purified by low-temperature crystallization.

Anal. Found: C, 63·93; H, 8·33; S, 11·36. $C_{15}H_{22}O_3S$ requires C, 63·80; H, 7·85; S, 11·35 per cent.

Kinetic measurements were performed as described elsewhere.[2]

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* Analysis by Micro-Tech Laboratories, Skokie, Illinois.
† Texas Company Fellow, 1954–1956.

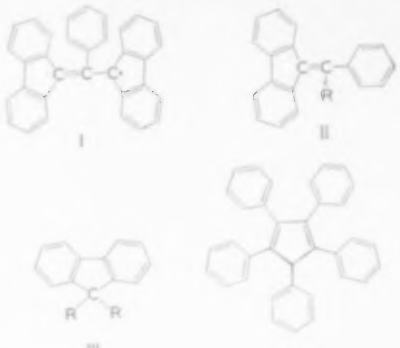
[6] C. K. Ingold *Structure and Mechanism in Organic Chemistry* Chaps. VII and VIII. Cornell University Press, Ithaca, N. Y. (1953).
[7] P. B. D. de la Mare and C. A. Vernon *J. Chem. Soc.* 41 (1956).
[8] S. Winstein, D. Darwish and J. Takahashi Private communication.
[9] R. S. Tipson *J. Org. Chem.* **9**, 235 (1944).

Resonance energies of two unusually stable hydrocarbon free radicals

(*Received* 24 *August* 1957)

The radical α,γ-bisdiphenylene-β-phenylallyl (I) was first prepared by Koelsch in 1932.[1] Its stability is such that it reacts only slowly with molecular oxygen,[1,2] but electron spin resonance (ESR) measurements[2] have completely confirmed its radical nature.[2] In benzene solution I shows 1·1 radicals per mole by comparison of the integrated intensity of its ESR spectrum with that of diphenylpicrylhydrazyl.[3] The pentaphenyl*cyclo*pentadienyl radical (IV) is also reported[3] to be much more stable than the triphenylmethyl radical toward reaction with molecular oxygen and toward dimerization, although it does not appear to be quite as stable as I.[4] The present note reports that the great stability of I and IV toward reaction with molecular oxygen and toward dimerization is completely accountable on the basis of their resonance energies, as calculated by the simple L.C.A.O.M.O. method.[5]

[1] C. F. Koelsch *J. Amer. Chem. Soc.* **79**, 4439 (1957).
[2] J. E. Wertz and J. L. Vivo Acrivos Unpublished results.
[3] K. Ziegler and B. Schnell *Liebigs Ann.* **445**, 266 (1925).
[4] J. Wertz Unpublished results.
[5] A. J. Streitwieser *J. Amer. Chem. Soc.* **74**, 5288 (1952). This paper contains very similar calculations and further references.



I II III IV

The increase in resonance energy (Δ D.E.) on forming I by dissociation of a group from the position marked with a dot is given by the π-electron delocalization energy of I less that of II and that of III. Δ D.E. for I calculated in this way is $2{\cdot}84\beta$ and Δ D.E. calculated for IV in a similar manner is $3{\cdot}23\beta$.* For comparison the much less stable triphenylmethyl radical has ΔD.E. $= 1{\cdot}80\beta$.[5] Thus I and IV have predicted resonance energies greater than that of the triphenylmethyl radical by about one β (the carbon–carbon resonance integral) or more. An appropriate value for β is thought to be about 20 kcal/mole.[6]

The fact that IV is calculated to have the higher resonance energy while I actually appears to be somewhat more stable may be due to steric inhibition to coplanarity in IV.

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* Numerical calculations were performed on the Remington Rand "Univac" by the Numerical Analysis Laboratory of the University of Minnesota.

[6] C. A. Coulson *Valence* p. 240. Clarendon Press Oxford (1953).

Relation between the "regular" and Kekulé structures for benzene

(*Received* 3 *September* 1957)

IN *Chemistry and Industry* p. 1520 (1955), it was shown that Pauling's bond energies can be used to arrive at the conclusion that the distribution of energy about each carbon atom in benzene is symmetrical. This cannot, of course, be so in the Kekulé structure. However, it is remarkable that the resultant of two forces of magnitude 58·6 and 100 (corresponding to the Pauling bond energies of single and double carbon—carbon bonds respectively) acting at 120° (the angle between the carbon—carbon bonds in both the regular and Kekulé rings) has a magnitude of 87·2 i.e. very near to the 87·3 kcal assigned as the energy of the C—H bond. For equilibrium to be attained at each carbon, the C—H bond direction would have to form an angle of approximately 144° with that of the C—C bond of the ring.

It is possible, therefore, to picture the change of Kekulé to regular structure as involving shortening and lengthening of the single and double bonds respectively, accompanied by a change in the direction of the C—H bonds.

Another remarkable feature to be detected by the present approach is that the pair of values 58·6 and 100 are very near the possible limits permitted by the equation

$$P^2 + Q^2 - PQ = 87{\cdot}2^2$$

If $P = 100$ and $Q = 58{\cdot}6$, the equation is valid. For all values of P between 100 and 87·2 (when it becomes equal to Q) a corresponding value of Q can be calculated, but when P reaches or exceeds 100·6 no corresponding value for Q is possible. This suggests that distortion of the regular to the

Kekulé structure is the limit of possible distortion. It can hardly be assumed that the Pauling bond energy values have such a degree of accuracy that this conclusion is out of the question.

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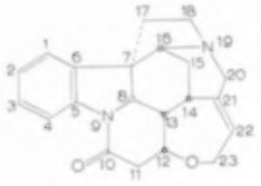
Stereochemical control of some reactions of strychnine

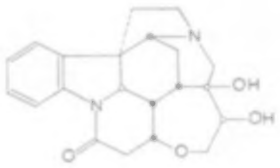
(*Received* 16 *September* 1957)

IN the elucidation of the structure of strychnine, Robinson's interpretation of an extended series of reactions carried out by Leuchs was of crucial importance.[1,2] The mechanisms of these reactions have remained obscure, but may now be explained by taking account of the stereochemistry of strychnine and its products. The relative configurations at the asymmetric centres of strychnine have been shown from chemical[3] and X-ray diffraction[4] evidence to be as indicated in (I). Hydrogen atoms above the plane of the molecule (β) have been represented by closed circles; below (α), by open circles. Bonds coming above the plane of the molecule have been represented by solid lines; below, by broken lines. Recently, it has been shown[5] that the absolute configuration of strychnine is the reverse of that indicated in (I).

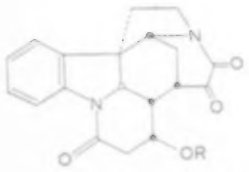
A model of (I) shows the underside of the double bond to be turned in towards the centre of the molecule, and hence protected from attack.[3] This may explain why chlorine[6] and bromine,[7] which generally add *trans*,[8] leave it unaffected, and attack the aromatic ring. The only addition reactions of the double bond thus far noted, hydroxylation by permanganate[9] and hydrogenation[10] both involve



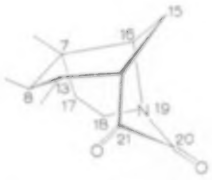
I



II



III



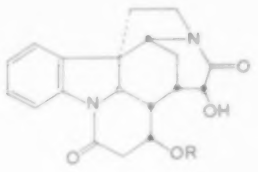
IV

[1] R. Robinson *Proc. Roy. Soc.* A **130**, 431 (1931).
[2] R. Robinson *Progress in Organic Chemistry* (Edited by J. W. Cook) Vol. 1, p. 1. Butterworths, London (1952).
[3] H. L. Holmes *The Alkaloids* (Edited by R. H. F. Manske and H. L. Holmes) Vol. II, p. 536. Academic Press, New York (1952).
[4] J. H. Robertson and C. A. Beevers *Acta Cryst.* **4**, 270 (1957); C. Bokhoven, J. C. Schoone and J. M. Bijvoet *Ibid.* **4**, 275 (1957).
[5] A. F. Peerdeman *Ibid.* **9**, 824 (1956).
[6] H. Leuchs and K. Steinborn *Ber. Dtsch. Chem. Ges.* **71**, 1577 (1938).
[7] H. Leuchs and P. Boll *Ibid.* **43**, 2362 (1910).
[8] C. K. Ingold *Structure and Mechanism in Organic Chemistry* p. 658. Bell and Sons, London (1953).
[9] M. Kotake and T. Mitsuwa *Bull. Chem. Soc. Japan* **11**, 231 (1936); V. Prelog and A. Katheriner *Helv. Chim. Acta* **31**, 505 (1948).
[10] A. Skita and H. H. Franck *Ber. Dtsch. Chem. Ges.* **44**, 2862 (1911); A. E. Oxford, W. H. Perkin and R. Robinson *J. Chem. Soc.* 2389 (1927).

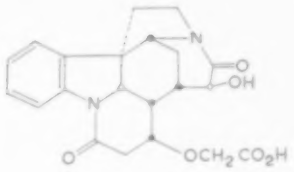
cis addition.[11] Hence it seems certain that dihydroxystrychnine from the former reaction has the configuration shown in (II).[3]

More prolonged oxidation with potassium permanganate affords strychninonic acid (III; R = CH_2CO_2H).[12] The newly formed δ-lactam ring is relatively unstable to hydrolysis,[13] because the atoms C_{16}, C_{18} and C_{21} cannot all be in the same plane as the amide linkage[14] (see perspective partial formula (IV)).

Reduction of the carbonyl group (C_{21} = O) of strychninonic acid by either catalytic hydrogenation[15] or sodium amalgam[16] probably involves addition to the more accessible top-side of the molecule, so that strychninolic acid has the formula (V; R = CH_2CO_2H). The epimeric dihydrostrychninonic acid, formed in small yield with strychninonic acid in the permanganate oxidation,[12] is accordingly formulated as (VI).

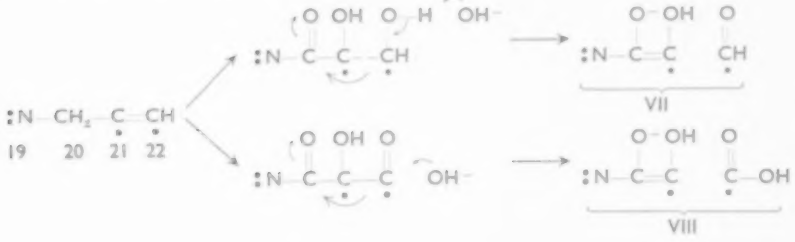


V



VI

Holmes[3] adduced as further evidence for the configuration at C_{21} in dihydrostrychninonic acid the similar configuration in dihydroxystrychnine (II), which may be an intermediate. However, the configuration of any intermediate is probably irrelevant, since the formation of dihydrostrychninonic acid involves a hydrolysis of C_{21}–C_{22} at some stage [C_{21} gains both a hydroxyl group *and a hydrogen atom*, and so the change from strychnine is not an oxidation alone]. The only plausible mechanisms[1] for this hydrolysis are those shown leading to the enolic form of dihydrostrychninonic acid (VIII) or of an aldehydic precursor (VII). Either mechanism involves the formation of the enolate ion IX, in



which the asymmetry at C_{21} is lost. The protonation of this enolate ion will, for stereoelectronic reasons,[17] lead to the formation of a quasi-axial C_{21}-hydrogen bond, giving the configuration shown in (VI) (partial perspective formula (X)).

Models of strychninolic acid (V; R = CH_2CO_2H) and hydroxydihydrostrychninolone-A (V; R = H), set up with the Courtaulds' atomic models,[18] show the α-oriented C_{21} hydroxyl group to be pressing against the C_{12} oxygen atom. In dihydrostrychninonic acid (VI) there is only minor steric compression of the C_{12} oxygen atom from the α-oriented C_{21} hydrogen atom; while in strychninonic acid (III; R = CH_2CO_2H) and hydroxydihydrostrychninone-A (III; R = H) there is no interference

[11] L. Crombie *Quart. Rev. Chem. Soc., Lond.* **6**, 101 (1952).
[12] H. Leuchs *Ber. Dtsch. Chem. Ges.* **41**, 1711 (1908).
[13] H. Leuchs and P. Reich *Ibid.* **43**, 2417 (1910); H. Leuchs and L. E. Weber *Ibid.* **42**, 3703 (1909).
[14] L. Pauling, R. B. Corey, and H. R. Branson *Proc. Nat. Acad. Sci., Wash.* **37**, 205 (1951).
[15] V. Prelog and S. Szpilfogel *Helv. Chim. Acta* **28**, 1669 (1945).
[16] H. Leuchs and W. Schneider *Ber. Dtsch. Chem. Ges.* **42**, 2494 (1909).
[17] E. J. Corey and R. A. Sneen *J. Amer. Chem. Soc.* **78**, 6269 (1956).
[18] G. S. Hartley and C. Robinson *Trans. Faraday Soc.* **48**, 847 (1952).

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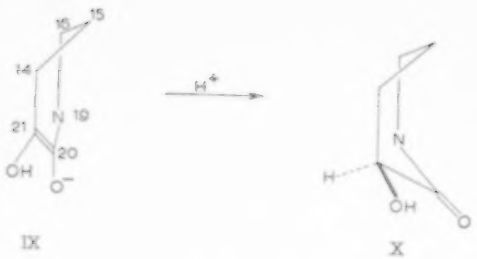
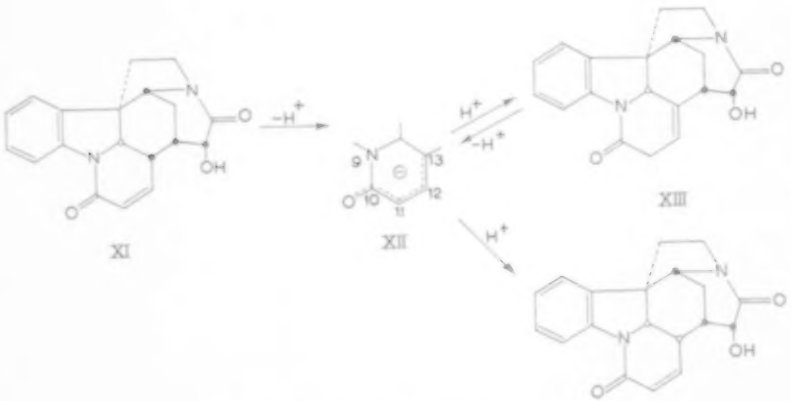


IX X

between the C_{12} oxygen atom and the C_{21} carbonyl oxygen. The different degrees of steric compression may explain the varying ease of elimination of the C_{12} oxygen function in forming an $\alpha\beta$-unsaturated lactam[19] [(V; R = CH_2CO_2H)[16] > (V; R = H)[20] > (VI)[21] > (III; R = CH_2CO_2H), (III; R = H)[20]]. The especially easy elimination from strychninolic acid (V; R = CH_2CO_2H) to give strychninolone-A (XI) is probably facilitated by the inductive effect of the carbonyl group.

It has been suggested previously[22] that strychninolic acid eliminates glycollic acid more readily than does dihydrostrychninonic acid because only in the former is hydrogen bonding between the C_{21} hydroxyl group and the outgoing C_{12} oxygen atom possible. Such an explanation does not explain why the same order of reactivities is found in the acid-catalysed elimination,[20] which must involve protonation of the C_{12} oxygen, and in which consequently hydrogen-bonding by the hydroxyl group cannot be significant.



XI XII XIII XIV

When treated with bases, strychninolone-A (XI) isomerises to strychninolone-B (XIII);[21] more drastic treatment results in further isomerisation to strychninolone-C (XIV),[21,23] which differs from strychninolone-A only in configuration at C_{12}.[24] On models it can be seen that in strychninolone-C the chain of atoms N–C_{12} has become more nearly coplanar with the benzene ring than it is in strychninolone-A. The increased resonance consequent on greater planarity would explain the greater thermodynamic stability of strychninolone-C, the lessened reactivity of its Δ^{11} double bond (e.g. to the addition of hydrazine[20]), and the bathochromic shift in absorption (strychninolone-A, λ_{max} = 282 mμ; strychninolone-C, λ_{max} = 297 mμ).[3]

[19] Cf. J. Kenner *Chem. & Ind. (Rev.)* 727 (1955).
[20] J. T. Edwards and R. Robinson *Tetrahedron* **1**, 28 (1957).
[21] H. Leuchs and G. Schwaebel *Ber. Dtsch. Chem. Ges.* **47**, 1552 (1914).
[22] R. B. Woodward Quoted in reference 3.
[23] H. Leuchs and W. Bendixsohn *Ber. Dtsch. Chem. Ges.* **52**, 1443 (1919).
[24] V. Prelog, S. Szpilfogel and J. Battegay *Helv. Chim. Acta* **30**, 366 (1947).

The formation of strychninolone-B before the more thermodynamically stable strychninolone-C is an example of kinetic control, the addition of a proton to the common intermediate anion(X) taking place more rapidly at the centre of the mesomeric system.[25]

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[25] G. A. R. Kon and E. A. Speight *J. Chem. Soc.* 2727 (1926); C. K. Ingold, E. de Salas and C. L. Wilson *Ibid.* 1328 (1936); A. J. Birch *Ibid.* 1551 (1950); R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore *J. Amer. Chem. Soc.* **74**, 4223 (1952).

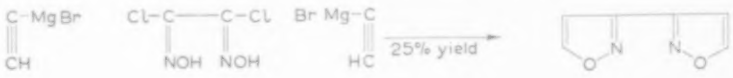
Synthesis of 5:5′-bi-*iso*xazole

(*Received* 8 *November* 1957)

ALTHOUGH a number of substituted bi-*iso*xazole derivatives have been reported in the literature, none of the six fundamental members (I) which are theoretically possible was known until 1957. Only

I

quite recently[1] we succeeded in synthesising 3:3′-bi-*iso*xazole (III), which is formed when ethynylmagnesium bromide acts on dichloroglyoxime (II), according to scheme:

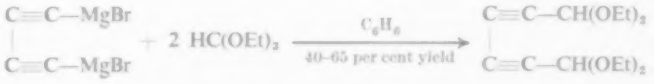


II III

In the performance of experiments aimed to the preparation of the other possible isomers, we have now synthesised 5:5′-bi*iso*xazole (V), which is obtained in excellent yield on treatment of hexadiindial tetraethylacetal (IV) with hydroxylamine hydrochloride:

IV V

Grard[2] has reported the preparation of (IV) by oxidation of propargylic aldehyde acetal. Since the preparation of the latter is difficult and the yield of (IV) poor, a new synthesis of (IV) has been achieved by condensation of diacetylene magnesium bromide[3] with ethyl orthoformate:



5:5′-Bi-*iso*xazole (V) is a crystalline solid m.p. 116–117·5° (the 3:3′-isomer melts at 73–73·5°) of faint pleasant odour. It is volatile in steam, and soluble in most organic solvents. Its chemical

[1] A. Quilco, G. Gaudiano and A. Ricca *Gazz. Chim. Ital.* **87**, 638 (1957).
[2] G. Grard *C. R. Acad. Sci., Paris* **189**, 925 (1929).
[3] F. Bohlman *Chem. Ber.* **84**, 553 (1951).

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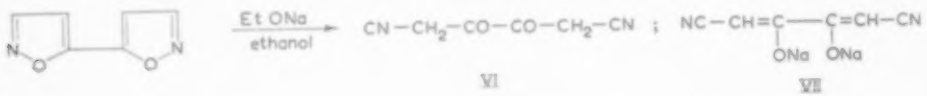
behaviour corresponds to that of simple *iso*xazoles with a free 3-position: accordingly, it is readily isomerized by alkaline alkoxides solutions giving the sodium salt (VII) of 3:4-diketoadipic nitrile (VI).



VI VII

Whereas the sodium salt, which probably possesses structure (VII), is very stable in alkaline solutions, the free diketonitrile (VI) appears to be extremely labile. Aqueous solutions of (VII) turn rapidly to orange-red and then to brown when treated at ordinary temperature with dilute acids, owing to the formation of condensation products.

The study of the chemical and spectrochemical behaviour of the two symmetrical bi-*iso*xazoles is in progress, and will be reported later.

EXPERIMENTAL

Hexadiindial tetraethylacetal (IV). Diacetylene (4·5 g) dissolved in anhydrous ether (15 ml) was slowly introduced, under continual stirring, into a cooled solution of ethylmagnesium bromide prepared from 6 g of magnesium. After the addition of the diacetylene, the reaction mixture was stirred for at least 1 hr at room temperature, when most of the solvent was distilled. Towards the end, the temperature of the bath was allowed to rise to 60°, and maintained for 5–10 min. Ethyl orthoformate (48 g) dissolved in 50 ml of dry benzene was then introduced over a period of 10 min under continual cooling and stirring. The reaction was completed by refluxing at 70–80° for 1¼ hr. The brown semi-solid reaction mixture was poured into a solution of 20–30 g of ammonium acetate in 500 ml of ice-water. The benzene layer was separated and the aqueous layer extracted with ether. The combined organic extracts, dried over K_2CO_3, gave, after removal of the solvent and the unchanged orthoformate by distillation at ordinary pressure, 10–15 g of a liquid b.p. 142°/2 mm, with n_D^{22} 1·4686. Yield 40–65 per cent (Found: 66·09; H, 8·69. Calc. for $C_{14}H_{22}O_4$: C; 66·1; H, 8·7 per cent). According to Grard, hexadiindial tetraethylacetal has b.p. 140–141°/3 mm and n_D^{22} 1·4638.

5:5′-*Bi*-iso*xazole* (V). To a solution of 3·4 g of (IV) in 34 ml of ethanol, 4·3 g of $NH_3O.HCl$ dissolved in 7 ml of water were added. After ½ hr refluxing on the water-bath most of the alcohol was removed *in vacuo* at ordinary temperature and the residue distilled in steam. The aqueous distillate (600–700 ml), which contains the bi-*iso*xazole partly dissolved and partly in solid crystalline form, was saturated with ammonium sulphate and then extracted with ether. The extract, dried over Na_2SO_4, gave after removal of the solvent 1·6 g of nearly pure 5:5′-bi-*iso*xazole. Yield 86 per cent. Recrystallised from ethanol it forms beautiful needles m.p. 116–117·5° (Found: N, 20·6. Calc. for $C_6H_4O_2N_2$: N, 20·5 per cent).

5:5′-Bi-*iso*xazole has a characteristic not unpleasant odour, similar to that of the 3:3′-isomer. It is readily soluble in warm alcohol, benzene and chloroform, and can be recrystallised from boiling water in which it is slightly soluble at ordinary temperature.

Isomerisation to 3:4-*diketoadipic nitrile* (VI). 5:5′-Bi-*iso*xazole (0·5 g), dissolved in 8 ml of warm anhydrous ethanol, was introduced into the cooled Na-ethoxide solution prepared from 0·5 g of Na in 15 ml of ethanol. A gelatinous precipitate of diketoadipic nitrile sodium salt (VII) separated immediately with evolution of heat and on keeping, and more rapidly on gentle heating, became crystalline. The filtered solid was washed with absolute alcohol and dried in *vacuo* over P_2O_5. Yield 0·65 g (theoretical for the anhydrous disodium salt 0·66 g).

The salt was purified by dissolving in 3–4 ml of water and subsequent precipitation with 80 ml of anhydrous ethanol. It forms crops of small needles, readily soluble in water; the solution giving an intense dark red enolic reaction with $FeCl_3$. The analysis indicates that the salt contains two molecules of water (Found: N, 13·0; Na, 22·1. Calc. for $C_6H_2O_2N_2Na_2{\cdot}2H_2O$: N, 12·9; Na, 21·9 per cent). One molecule is easily eliminated by heating at 110° *in vacuo* over P_2O_5 (loss of weight: found 8·9, calc. for Na_2-salt, $2H_2O \rightarrow Na_2$-salt, H_2O 8·3 per cent). The analysis of the partially dehydrated salt: (Found: N, 14·4; Na, 23·2. Calc. for $C_6H_2O_2N_2Na_2$, H_2O: N, 14·1; Na, 23·2 per cent).

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Tetrahedron, 1958, Vol. 2, pp. 361–366. Pergamon Press Ltd., London

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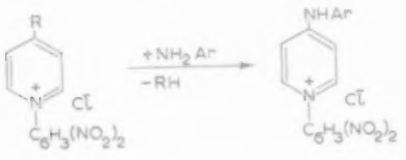
PRELIMINARY COMMUNICATIONS

New conversions of pyridinium salts and syntheses of γ-amino-substituted pyridines*

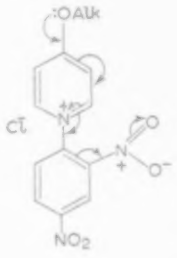
(*Received* 31 *July* 1957)

In an earlier paper an attempt to effect the pyridine ring cleavage in γ-alkoxy-, phenoxy- and methylmercapto-substituted pyridines by treating N-2, 4-dinitrophenylpyridinium chlorides(I) with aromatic amines was described.[1] The results showed that the pyridine ring does not open, the arylamino group being substituted for γ-alkoxy(methylmercapto-, phenoxy) group, to form N-2,4-dinitrophenyl-γ-arylamino pyridinium chlorides (II), as follows:



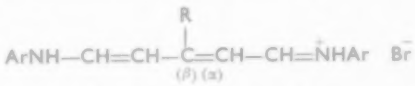
I II

R: AlkO−, CH_3S−, C_6H_5O−



V

Later the cleavage of the pyridine ring in γ-alkoxy (methylmercapto-, phenoxy)pyridines was effected by treating these compounds with cyan bromide and aromatic amines.[2] β-Alkoxy(methylmercapto-, phenoxy) substituted glutaconaldehyde anil anilide hydrobromide (III) were obtained.



III

R:AlkO—, CH_3S—, C_6H_5O—.

Of these compounds the β-alkoxy have been shown to be highly unstable even in crystalline state.† Particularly unstable are their alcoholic solutions, which quickly decolorise when heated. The preparations on being stored, especially in summer time, gradually turn into yellowish crystalline line substances impregnated with liquid. The β-phenoxyglutaconaldehyde anil anilide hydrobromide is somewhat more stable. Yet it also decomposes on heating or when stored for a long time.

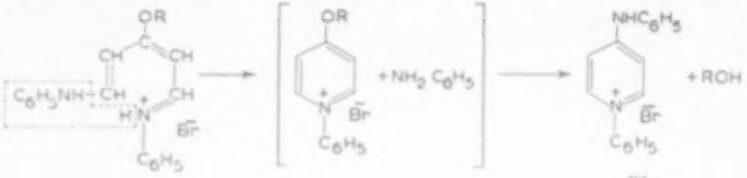
Investigation of the crystalline products obtained from the conversion of anil anilide salts (III; Ar = C_6H_5-, R = —OAlk, —OC_6H_5) showed them to be the same compound, namely N-phenyl-γ-phenylamino pyridinium bromide (IV), obtained as pale yellow hygroscopic needles, m.p. 192–193°.

* Translated by A. L. Pumpiansky, Moscow.

† This seems to have been the reason why Ebert did not succeed in effecting the cleavage of γ-methoxypyridine with cyan bromide and aniline. He failed to isolate β-methoxyglutaconaldehyde anil anilide hydrobromide.[3]

[1] A. F. Vompe, N. F. Turitsyna and I. I. Levkojev *Dokl. Akad. Nauk SSSR* **65**, 839 (1949).
[2] A. F. Vompe *On the cleavage of pyridine bases* D.Sc. Thesis, Moscow (1951).
[3] G. Ebert Dissertation, Dresden (1913).

(Found (after drying *in vacuo* at 40–50°): N, 8·52, 8·39; Br, 24·45, 24·68. Calc. for $C_{17}H_{15}N_2Br$: N, 8·57; Br, 24·44%). The formation of compound (IV) proceeds according to the general scheme:



IV

R: CH_3-, ... iso $C_5H_{11}-$, C_6H_5- etc.

The products of decomposition of the β-phenoxyderivative (III) were found to contain phenol. Thus, the cyclisation reaction of glutaconaldehyde anil anilide salts into N-arylpyridinium salts, due to Zincke, which usually requires rigid conditions (melting, heating with concentrated hydrochloric acid, etc.),[6] proceeds very readily in this particular case.

Conversions studied can be considered as part of the general substitution reaction of γ-alkoxy-(phenoxy) groups by the aromatic amine substituents in pyridinium salts containing electronegative radicals ($C_6H_3(NO_2)_2$-, C_6H_5-) at the cyclic nitrogen (cf. ref. 1). Undoubtedly one is dealing with the conjugation of *p*-electrons of the oxygen atom in the —OAlk(—OC_6H_5) group with the other part of the pyridinium salt molecule (see e.g. V) that imparts to these molecules the oxonium salt properties. (cf. ref. 5).

β-Methylmercaptoglutaconaldehyde anil anilide hydrobromide (III; Ar = C_6H_5-, R = —SCH_3) readily undergoes cyclisation, the reaction, however, ceasing at the stage of N-phenyl-γ-methylmercaptopyridinium bromide formation. Such a reaction is easy to understand if one bears in mind that the sulphur atom in N-phenyl-γ-methylmercaptopyridinium bromide is partly in the onium state (anologically V) sulphonium salts being less reactive than those of oxonium.

The increase of the electronegativity of the radical linked with the nitrogen atom in γ-methylmercaptopyridine (due to the dinitrophenyl radical being substituted for the phenyl one) results in the amine substituent being substituted for the methylmercapto group, N-2,4-dinitrophenyl-γ-methylmercaptopyridinium chloride reacting with aromatic amines, though somewhat slower than γ-alkoxyderivatives (cf. 1).

The problem of the lability of the alkoxy group in N-alkyl-γ-alkoxypyridinium halide was next investigated. The reaction of γ-methoxypyridine methiodide with aniline (in alcoholic solution when heated on a water-bath) results in the removal of methyl iodide and formation of N-methyl-γ-pyridone, no γ-phenylaminopyridine methiodide being found. It follows that to render the alkoxy group capable of being substituted it is not sufficient to make the cyclic nitrogen atom assume the tetravalent state but this atom must in addition be linked to an electronegative radical.

VI

Ar: C_6H_5- (94–96), (p) $CH_3C_6H_4-$ (86), (o) $CH_3C_6H_4-$ (~58), (p) ClC_6H_4- (~73), (p) $CH_3OC_6H_4-$ (83), α-$C_{10}H_7-$ (42) */

* The percentage yields of γ-arylaminopyridines (VI) are indicated in brackets.

The possibility of substituting the phenoxy group in γ-phenoxypyridine methiodide by aromatic amine substituents was investigated. The splitting off of the aryl halide (under the action of aromatic amine) seemed in this case to be unlikely. Heating γ-phenoxypyridine methiodide with aniline at 115–120° yielded γ-phenylaminopyridine methiodide in 88 per cent yield.

[6] Th. Zincke, G. Heuser and W. Möller *Liebigs Ann.* **333**, 328 (1904).

[1] H. Meerwein, G. Hinz, P. Hofman, E. Kroning and E. Pfeil *J. Prakt. Chem.* **147**, No. 2, 257 (1937); H. Meerwein, E. Battenberg, H. Gold, E. Pfeil and G. Willfang *J. Prakt. Chem.* **154**, No. 2, 83 (1939)

It has also been found that the exchange of the arylamino group for the phenoxy group takes place readily when heating the mixture of γ-phenoxypyridine hydrohalide and the aromatic amine or the salt of the amine and γ-phenoxypyridine. No exchange of the phenoxy group takes place when heating the mixture of the salts of γ-phenoxypyridine and aromatic amines. It has thus been shown that both γ-phenoxypyridinium cation and the free amine participate in the reaction. This naturally suggested carrying out the reaction of γ-phenoxypyridine with the salts of aliphatic amines as well as with ammonium salts, e.g. ammonium chloride. It has been found that the phenoxy group can in this way be substituted by the amino group or substituents of primary and secondary aliphatic amines. Thus, on fusing γ-phenoxypyridine and *cyclo*hexylamine hydrobromide at 200–210° for 1 hr, γ-*cyclo*hexylaminopyridine was obtained in 72 per cent yield (colourless prisms from ether), m.p. 147–148°. Found: N, 15·87, 16·05. Calc. for $C_{11}H_{16}N_2$: N, 15·90%). Similarly γ-dimethylaminopyridine was synthesised by heating γ-phenoxypyridine with dimethylamine hydrobromide for 1 hr at 190–200°. Yield 82 per cent (colourless plates m.p. 112–113°; picrate m.p. 204–206°. (cf. ref. 6)

It has also been found that heating γ-phenoxypyridine with ammonium chloride in an open vessel at 300–310° for 1 hr gives γ-aminopyridine yield 90–95 per cent. To extract γ-aminopyridine from the aqueous solution, use was made of *n*-butanol, which simplifies the isolation of the base.

The preparation of γ-aminopyridine by this method is simpler and more convenient than the syntheses of Koenigs and Greiner[7] and Hertog and Overhoff.[8] These, cannot be used to synthesise γ-aminopyridines substituted on the amino group, whilst the reaction now investigated can be successfully applied as a general procedure for obtaining various γ-aminosubstituted pyridines.

It is to be noted that γ-phenoxypyridine reacting with amine salts behaves similarly to 9-phenoxyacridine.[9] This analogy could, however, hardly be foreseen as 9-alkoxyacridines are known to react with amine salts differently from γ-alkoxysubstituted pyridines and quinolines.[10]

At the conclusion of this investigation a paper by Jerchel *et al.*[11] appeared dealing with the reaction of γ-pyridyl-pyridynium salts, in which the possibility of synthesising γ-aminopyridine from the reaction of γ-phenoxypyridine and ammonia was indicated. No experimental details were given.

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N. V. Monitch
N. F. Turitsyna
L. V. Ivanova

[6] E. Koenigs, H. Friedrich and H. Jurany *Ber. Dtsch. Chem. Ges.* **58**, 2275 (1925).
[7] E. Koenigs and H. Greiner *Ber. Dtsch. Chem. Ges.* **64**, 1054 (1931).
[8] H. J. den Hertog and J. Overhoff *Rec. Trav. Chim.* **69**, 468–473 (1950); cf. E. Ochiai *J. Org. Chem.* **18**, 534 (1953).
[9] N. S. Drosdov and O. M. Tcherntsov *Zh. Obsch. Khim.* **5**, 1736 (1935).
[10] H. J. Barber, J. H. Wilkinson and W. G. H. Edwards *J. Soc. Chem. Industr.* **66**, 411 (1947).
[11] D. Jerchel, H. Fischer and K. Thomas *Chem. Ber.* **89**, 2921 (1956).

The structures of jaconecic and *iso*jaconecic acids

(*Received* 17 *September* 1957)

Jaconecic acid ($C_{10}H_{16}O_6$) to which we have tentatively assigned structure (I),[1,2] has been more recently obtained from the alkaloid tomentosine ($C_{19}H_{27}O_7N$) by Adams, Gianturco and van Duuren[3] who propose, without additional evidence structure (II).

*iso*Jaconecic acid ($C_{10}H_{16}O_6$), which together with jaconecic acid is obtained from jacobine, jaconine and the chlorodilactone ($C_{10}H_{13}O_4Cl$), would also be an expected product from the alkaline

[1] R. B. Bradbury *Chem & Ind. (Rev.)* 1021 (1954).
[2] R. B. Bradbury and J. B. Willis *Aust. J. Chem.* **9**, 258 (1956).
[3] R. Adams, M. Gianturco and B. L. van Duuren *J. Amer. Chem. Soc.* **78**, 3513 (1956).

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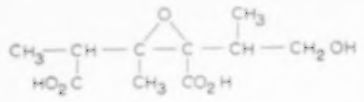
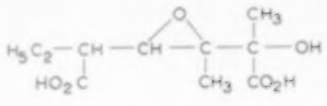


I



II

hydrolysis of tomentosine[3] and othosenine,[4] but was apparently overlooked by the American[5] and Russian[6] workers.

This report concerns the reactions of jaconecic and *iso*jaconecic acids with ferric chloride, acetic anhydride and lead tetra-acetate, which were, amongst other results previously regarded[3] as conflicting with formula (I). Pure jaconecic and *iso*jaconecic acids give negative and positive reactions respectively with ferric chloride, and previously obtained faint positive reactions with jaconecic acid must have been due to contamination with *iso*jaconecic acid. That *iso*jaconecic acid is an α-hydroxy acid and the oxygen atom α- to the carboxyl group in jaconecic acid is part of an oxygen containing ring is confirmed by periodic acid oxidation of the lithium aluminium hydride reduction products ($C_{10}H_{20}O_4$) of dimethyljaconecate and dimethyl*iso*jaconecate which consume 0·2 and 1·3–1·8 mol. per mol. substance respectively, and the reduction product from dimethyl*iso*jaconecate yields formaldehyde. Jaconecic acid with acetic anhydride gives an acetate anhydride ($C_{12}H_{16}O_6$) which indicates, should Blanc's rule be valid, that it contains three or fewer carbon atoms between the carboxyl groups, and cannot be represented by formula (II). This is further confirmed by the reaction of jaconecic acid with lead tetra-acetate at 100°, which yields carbon dioxide, acetaldehyde, (+) β-methyllaevulinic acid (III) and (+) β-methyl-γ-carboxy-γ-valerolactone (IV), derivatives of the last two products being compared with synthetic specimens.

However *iso*jaconecic acid under the same conditions yields a keto-acid $C_9H_{14}O_4$ (V), which although it forms a normal semicarbazone breaks down with 2 : 4-dinitrophenylhydrazine in 2 N hydrochloric acid to a derivative of methylacetoacetic acid. However attempts to prepare an authentic specimen of this derivative results in the formation of the pyrazolone.

It has previously been shown[6] that nitric acid oxidation of jaconecic acid yields α, β-dimethylmalic acid and two other dibasic acids $C_9H_{14}O_6$ and $C_9H_{12}O_7$, whilst *iso*jaconecic acid is but slightly attacked under the same conditions.[7]

To formulate jaconecic and *iso*jaconecic acids it is logical to attempt to add three carbon and one oxygen atoms to the largest identified fragment: β-methyl-γ-carboxy-γ-valerolactone (IV), so that three carbon methyl groups result, and the oxygen atom can (1) form a second five membered ring with the γ-carboxyl group, (2) explain acetaldehyde formation and (3) be etherified in *iso*jaconecic acid and acetylated in jaconecic acid. The α- and β-positions are eliminated on the grounds that only one potential α-hydroxy acid group is present and that acetaldehyde formation is not explained. The only other alternative, the γ-position implies that the methyl group already present migrates from some other part of the molecule, and the formation of methylacetoacetic acid and α, β-dimethylmalic acid suggests the α-position as the source. This fixes the ring structure of the chlorodilactone (VI) in which the two rings are joined by one, rather than two carbon atoms as in formula (VII) proposed by Adams *et al.*[3] and the resemblance of (VI) to monocrotalic acid (X) which yields dimethylmaleic anhydride with nitric acid[8] is added confirmation. The structures now proposed for jaconecic acid (VIII), *iso*jaconecic acid (IX) and the chlorodilactone (VI), which were foreshadowed in our first paper[1] differ from those recently suggested[2] by the placement of a methyl group, which makes the hydroxyl group in (VIII) secondary rather than primary. No structure has yet been proposed by Adams for *iso*jaconecic acid and that given for jaconecic acid (II) and the chlorodilactone (VII) cannot be reconciled with our experimental results. The resistance of the tetrasubstituted glycidic acid grouping in jaconecic acid towards acid hydrolysis is paralleled by similar non-reactivity of the trisubstituted group in β-bromopicrotoxininic acid.[9]

Adams *et al.* have attributed the increased reactivity of jacobine compared with jaconecic acid towards hydrochloric acid, to the catalytic effect of the liberated base, but experiment has shown[7]

[4] E. S. Zhdanovich and G. P. Men'shikov *J. Gen. Chem., Moscow* **11**, 835 (1941).
[5] R. Adams and M. Gianturco *Angew. Chem.* **69**, 5 (1957).
[6] R. B. Bradbury *Aust. J. Chem.* **9**, 521 (1956).
[7] R. B. Bradbury Unpublished results.
[8] R. Adams and J. M. Wilkinson *J. Amer. Chem. Soc.* **65**, 2203 (1943).
[9] H. Conroy *J. Amer. Soc.* **79**, 1726 (1957).

that the chlorodilactone (VI) is not formed from jaconecic acid even in the presence of retronecine hydrochloride. A more plausible explanation would seem to be that conversion of jacobine, jaconine and the chlorodilactone to jaconecic acid involves inversion of configuration at the chlorine containing carbon atom,[10] and that this new configuration is less susceptible to carbonium ion formation (S_N1 mechanism[11]), or more likely to nucleophilic attack by chloride ion (S_N2 mechanism). The free carboxyl group by the formation of an internal salt (XI) might also render the epoxide group less accessible to attack. It is hoped to publish a full account of this work elsewhere.

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[10] S. Winstein and R. B. Henderson *Heterocyclic Compounds* (Edited by Elderfield) Vol. I, p. 11. Wiley, New York (1950); S. Winstein and H. J. Lucas *J. Amer. Chem. Soc.* **61**, 1576 (1939).
[11] F. A. Long, J. G. Pritchard and F. E. Stafford *J Amer. Chem. Soc.* **79**, 2362 (1957), and earlier papers.

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11-Alkylated steroids—I. The synthesis of 11-methylhydrocortisone acetate

(*Received* 7 *October* 1957)

THE unreactivity of an 11-ketone function in steroids to the usual carbonyl reagents is well known.[1,2] With the exception of a recent example of the formation of a steroid 11-cyclic acetal[3] only chemical or catalytic reduction to the 11-hydroxyl function[5,6] or to an 11-desoxy steroid[3,5] have been reported.

We wish to report the synthesis of 11-methylhydrocortisone acetate, illustrating the addition of an organometallic reagent to a steroid 11-ketone.

Treatment of 21-hydroxypregna-4,17(20)-[*cis*]-diene-3,11-dione acetate[6] with ethylene glycol and *p*-toluenesulfonic acid in refluxing benzene gave 21-hydroxypregna-5,17(20)-[*cis*]-diene-3,11-dione 3-ethylene acetal acetate (Ia), m.p. 160–162°.

Anal. Calcd. for $C_{25}H_{34}O_5$: C, 72·43; H, 8·27. Found: C, 72·11; H, 8·44. The compound was hydrolyzed with aqueous methanolic potassium bicarbonate to the free alcohol (Ib), m.p. 113·5–115°.

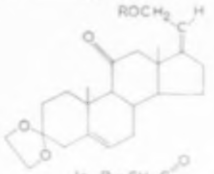
Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74·16; H, 8·66. Found: C, 74·05; H, 8·95. Reaction of Ib with triphenylmethyl chloride in dry pyridine at room temperature gave the 21-trityl ether (Ic), m.p. 201–203°.

Anal. Calcd. for $C_{42}H_{46}O_4$: C, 82·05; H, 7·54. Found: C, 81·99; H, 7·47. The latter was smoothly converted with a sixfold excess of methyllithium in benzene–ether at room temperature to 11β-hydroxy-11-methyl-21-triphenylmethoxypregna-5,17(20)-[*cis*]-dien-3-one ethylene acetal (II), m.p. 182–184°.

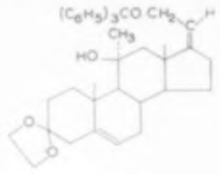
Anal. Calcd. for $C_{43}H_{50}O_4$: C, 81·87; H, 7·99. Found: C, 81·90; H, 7·95; γ_{max}^{Nujol} (cm^{-1}): 3480 (OH); 1672 (Δ^5); 1094, 1002 (C—O); 1596, 1492, 714, 698 (C_6H_5). (When methylmagnesium iodide was substituted for methyllithium only unchanged Ic was recovered. Attempted addition of

[1] D. H. R. Barton *Synthesis and Metabolism of Adrenocortical Steroids. Ciba Foundation Colloquia on Endocrinology* (Edited by W. Klyne) Vol. VII, p. 37. Little, Brown, Boston (1953).
[2] L. F. Fieser and M. Fieser *Natural Products Related to Phenanthrene* (3rd Ed.) pp. 409–410. Reinhold Publishing, New York (1949).
[3] B. J. Magerlein and R. H. Levin *J. Amer. Chem. Soc.* **77**, 1904 (1955).
[4] L. H. Sarett, M. Feurer and K. Folkers *Ibid.* **73**, 1777 (1951); N. L. Wendler, Huang-Minlon and M. Tishler *Ibid.* **73**, 3818 (1951); H. Heyman and L. F. Fieser *Ibid.* **73**, 5252 (1951); H. L. Herzog, M. A. Jevnik and E. B. Hershberg *Ibid.* **75**, 269 (1953); F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi *Ibid.* **75**, 1282 (1953).
[5] R. B. Moffett and J. H. Hunter *Ibid.* **73**, 1973 (1951).
[6] J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze and R. W. Jackson *Ibid.* **77**, 4436 (1955).

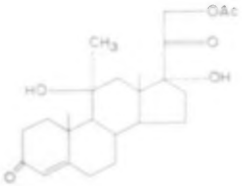
either the Grignard reagent or methyllithium to Ia or Ib gave only Ib.) Hydrolysis of II with dilute methanolic hydrochloric acid at room temperature removed both the trityl and ketol groups, giving 11β,21-dihydroxy-11-methylpregna-4,17(20)-[*cis*]-dien-3-one (IIIa), m.p. 188–192°.



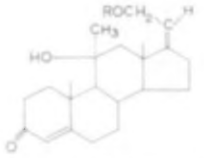
Ia R = $CH_3C(=O)$–
Ib R = H–
Ic R = $(C_6H_5)_3C$–



II



IV



IIIa R = H–
IIIb R = $CH_3C(=O)$–

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76·70; H, 9·36. Found: C, 76·35; H, 9·33. Treatment of IIIa with acetic anhydride pyridine at 25° C gave the corresponding 21-acetate IIIb, m.p. 109–112°.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74·57; H, 8·87. Found: C, 74·66; H, 8·97. When IIIb was treated with N-methylmorpholine oxide peroxide in *t*-butyl alcohol–pyridine containing a catalytic amount of osmium tetroxide,[7] there was obtained, in addition to unchanged IVb and more polar material, 11-methylhydrocortisone acetate (V), m.p. 191–195°.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68·87; H, 8·19. Found: C, 68·85; H, 8·22. γ_{max}^{Nujol} (cm^{-1}): 3400, 3345 (OH); 1744, 1724 (C=O); 1631 (conj. C=O), 1606 (Δ^4), 1232 (C–O acetate) λ_{max}^{EtOH} 243 mμ, a_M 16,350. This material reduced Tollens' reagent.

We have assigned the introduced 11-methyl group* the α-configuration largely on the basis of stereochemical considerations.

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JOHN A. HOGG

* Unpublished studies by Dr. J. C. Babcock of these Laboratories have shown that certain 11-oxo-androstanes undergo addition of methyl Grignard reagent as well as methyllithium to the 11-oxo group.

[7] W. P. Schneider and A.R. Hanze *U.S. Patent* 2,769,823 (November 6, 1956).

Tetrahedron, 1958, Vol. 2, p. 367. Pergamon Press Ltd., London

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BOOK REVIEW

J. VÈNE: **Chimie organique Générale.** Masson et Cie, Paris, 1957. 350 pp., 3.500 fr. (4.100 fr.).

THIS book, in French, attempts to describe that section of chemistry which concerns (a) the structure of organic compounds and the means for its determination, and (b) the reactivity of organic compounds and the mechanisms of their reactions. It is a book containing wide but elementary information on new developments in these fields, designed especially for those commencing the study of organic chemistry, or for those who studied the subject some 20–30 years ago and wish to bring their knowledge up to date. Considerations of space have contributed to limit the text to an outline of essentials, but copious references to original papers and to textbooks, monographs, and reviews are given to enable the reader further to pursue subjects of special interest.

The book is divided into five parts. Part 1 deals with classical molecular formulae and isomerism, Part 2 considers the relation between physical properties and molecular structure, Part 3 describes the nature of chemical bonds, Part 4 discusses organic chemical reactivity, and Part 5 surveys electronic interpretations of reactions.

The least satisfactory features of the book are Chapters I and II of Part 1, which are apt to be misleading in view of the treatment given to olefinic and acetylenic linkages in Chapter III; in the former, a description of isomerism and of the addition reactions of double bonds is given with elaborate illustrations in terms of tetrahedra, when the carbon atoms involved in fact possess planar trigonal sp^2-symmetry. The situation is the same for allene, in which the terminal carbon atoms have sp^2-symmetry, whilst the central carbon atom has the collinear *sp*-symmetry characteristic of the carbon atoms in acetylene. The same incorrect and misleading presentation occurs in Baeyer's strain theory; this is illustrated by the series of *cyclo*paraffins, which possess sp^3-tetrahedral symmetry, but ethylene, with sp^2-planar trigonal symmetry, is included as the first member of the series.

Apart from the foregoing shortcomings, the book gives an excellent picture of the field; thus it draws a clear distinction between polarisation and polarisability, and gives good, explicit statements concerning the π-component of the double bonds in C=O, C=N, and about the two π-components in C≡N, whilst it is emphasised that inductive and mesomeric effects for the same group can have opposite signs, although no statement is made that the energy sources of these two effects must therefore be different (electrostatic and quantum-mechanical, respectively). The book is remarkably free from errors; one such error occurs on page 10, where nitrogen is stated to be *either* 3- or 5- covalent. There are, however, some omissions. For example, there is no mention, in connexion with stereoisomerism, of the Fischer Convention; there is no reference to the recent work of Prelog on asymmetric synthesis leading to the deduction of absolute configuration; there is no reference to conformation and its effect on reaction velocity and equilibrium in *cyclo*hexanes (or in six-membered heterocycles such as piperidine and pyranose sugars), and there is no reference to the important contributions of Winstein on neighbouring group effects. It is to be hoped that some small additions on these topics will be made in a future edition.

With the above reservations, the book is strongly to be recommended to those who wish to learn something in outline of recent developments in theoretical organic chemistry.

C. W. SHOPPEE

Papers to be published in future issues

D. H. WHIFFEN and D. STEELE: Carbon–hydrogen stretching vibrations in fluoro*cyclo*-hexanes.

W. LANGENBECK: Über organische Katalysatoren—L. Entwicklungslinien der organischen katalysatoren.

A. BOWERS and H. J. RINGOLD: Steroids—XCII. Synthesis of halogenated steroid hormone-2. 6α- and 6β-fluoro-testosterone and 6α- and 6β-fluoro-progesterone.

C. CHEN: Estrane derivatives—I.

R. F. HUTTON and F. H. WESTHEIMER: N-methyl dihydronicotinamide.

N. L. WENDLER, R. P. GRABER and G. G. HAZEN: The Favorskii rearrangement in the formation of 17-methyl steroids. The configuration of C-17 bromides.

F. SCARDIGLIA and J. D. ROBERTS: Reactions of non-activated amyl halides with nucleophilic agents induced by alkali amides in liquid ammonia.

S. WINSTEIN, E. ALLRED, R. HECK and R. GLICK: Neighboring methoxyl participation in solvolytic nucleophilic substitution.

J. E. H. HANCOCK and H. W. TABER: The structure of Lagidze's *cyclo*butadiene derivatives—I. The "$C_{14}H_{10}$ hydrocarbon."

W. E. NOLAND and D. N. ROBINSON: Electrophilic substitution in skatole and its derivatives.

J. KENNER: Some mechanisms of oxidation.

D. HEINERT and A. E. MARTELL: Studies on pyridoxine and pyridoxal analogs—I. The synthesis of substituted pyridinealdehydes.

J. ROMO: The addition of hydrocyanic acid to Δ^{16}-pregnen-20-ones.

B. D. TILAK, M. K. UNNI and K. VENKATARAMAN: Anthraquinone and anthrone series—XXII. 3:4:9:10-Dibenzopyrene and pentaphene from Indanthrene scarlet 4G and Mayvat brilliant red AF.

H. RINGOLD and G. STORK: Steroids—XCIV. Synthesis of 2-methyl and 1, 2-dimethyl estrogens.

A. S. BAILEY and J. R. CASE: 4:6-Dinitrobenzofuroxan, nitrobenzofuroxan, and benzotrifuroxan; a new series of complex-forming reagents for aromatic hydrocarbons.

M. S. KHARASCH and G. SOSNOVSKY: Oxidative reactions of nitriles—I. Autoxidation.

M. S. KHARASCH and G. SOSNOVSKY: Oxidative reactions of nitriles—II. Reactions with *tert.*-butyl hydroperoxide.

F. GOGAN, A. E. O'BRIAN, E. M. PHILBIN, N. S. O'CONNOR, R. F. TIMONY and T. S. WHEELER: Claisen–Maase rearrangement of enol esters.

R. D. WILSON: Naphthaquinones—I. The molecular structures of some halogeno-2:7-dihydroxynaphthalenes.

A. K. GANGULY, T. R. SESHADRI and P. SUBRAMARIAN: A study of leucoanthocyanidins of plants—I. Isomers of leucodelphinidin from Karada bark and eucalyptus gum.

R. ANEJA, S. K. MUKERJEE and T. R. SESHADRI: Synthesis of benzo-furan derivatives—II. A new synthesis of visnagin.

T. KUTSUMA and S. SUGASAWA: Partial hydrolysis of diethyl γ,γ-diethoxycarbonylpimelate: a preparation of γ,γ-diethoxycarbonylpimelic acid.

W. COCKER, N. J. H. DODDS and T. B. H. MCMURRY: The chemistry of santonin—V. Some reduction products of 11β (H)-santonin.

A. SEIGEL, F. WESSELY, P. STOCKHAMMER, F. ANTONY und P. KLEZL: Über die Einwirkung von Alkalihydroxydlösungen auf *o*-Chinolacetate.

R. FUSCO and S. ROSSI: Asymmetric triazines—XII. Reaction of phosphorus pentachloride with 4-nitrosopyrazoles.

L. H. BRIGGS and R. C. CAMBIE: The extractives of *Vitex lucens*.

C. DJERASSI and O. HALPERN: Macrolide antibiotics—VII. The structure of neomethymycin.

G. R. CLEMO: Some aspects of the chemistry of cigarette smoke—I.

K. WIESNER, Z. VALENTA, W. A. AYER, L. R. FOWLER and J. E. FRANCIS: Annotinine—II. The complete structure.

H. HIRSCHMANN and F. B. HIRSCHMANN: C-22 ketals related to the sapogenins.

T. KUBOTA: Volatile constituents of black rotted sweet potatoes.

W. R. N. WILLIAMSON: The alkylation of pyrrolidine enamines.

V. M. MIĆOVIĆ and A. STOJILJKOVIĆ: The condensations of polyhydric alcohols and monosacchanides with *cyclo*pentanone and *cyclo*hexanone.

B. HELFERICH und M. BURGDORF: Über Derivate der D-Xylose.

E. LEETE: The biogenesis of annotinine.

R. T. CONLEY and F. A. MIKULSKI: Abnormal Beckmann rearrangements in polyphosphoric acid: benzil monoxime and benzoin monoxime.

D. LLOYD and J. S. SNEEZUM: The preparation of some pyridinium *cyclo*pentadienylides.

D. H. REID: Stable Π-electron systems and new aromatic structures.

G. WITTIG und V. SCHÖLLKOPF: Zum chemismus der Halogen–Lithium–Austauschreaktion.

D. T. ELMORE and J. R. OGLE: Acyl thiocyanates: on the nature of Clemmensen and Heitmann's "Glycollyl and lactyl thiocyanates".

G. I. FRAY: Reaction of phloroglucinol with sodium borohydride.

J. MEINWALD and O. L. CHAPMAN: The rearrangement of scopinone to meta-hydroxybenzaldehyde.

C. R. PATRICK: Some aspects of the thermochemistry and thermodynamics of fluorocarbons.

C. CHIURDOGLU et J. DECOT: Contribution a l'étude des composés sesquiterpéniques—II. Étude de la structure du bi*cyclo*vétivénol et du tri*cyclo*vétivénol, alcools primaires de l'essence de vétiver.

H. M. SMITH, J. M. SMITH and F. S. SPRING: The triterpenoids—LVI. The chemistry of the soyasapogenols A, B and C.

I. CHMIELEWSKA, J. CIEŚLAK, K. GORCZYŃSKA, B. KONTNIK et K. PIATKOWSKA: Structure de la yangonine. Étude spectrographique dans l'ultraviolet et l'infrarouge.

J. F. BIELLMANN, P. CRABBE et G. OURISSON: Le Diptérocarpol—II. Stéréochimie en C-13 et en C-17.

P. K. GROVER and T. R. SESHADRI: Preparation and constitution of *iso*pinastric acid.

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ERRATA

M. I. KABACHNIK, S. T. YOFFE and K. V. VATSURO
Tetrahedron **1**, 317–327 (1956).

The formula on p. 317 should be excluded.

On p. 218 reference 22 should refer to the second equation and "α-pyridon" should be referred to 23.

The legends to Fig. 1, on p. 320, should read:

I ethyl *cyclo*hexanonecarboxylate
II ethyl *cyclo*pentanonecarboxylate
III benzoylcamphor
IV ethyl acetoacetate
V ethyl benzoylacetate

1, 67 per cent methanol; 2, methanol; 3, chloroform; 4, ethanol; 5, benzene

On p. 323, the asterisk in the second line refers to the footnote marked with an asterisk on p. 322.

The legends to Fig. 4, on p. 325 should read as follows: Solvents: 1, 67 per cent methanol; 2, methanol; 3, ethanol; 4, benzene.

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